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Obsession

THE GENETIC AND ENVIRONMENTAL ARCHITECTURE OF OBSESSIVE-COMPULSIVE SYMPTOMS

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Lewis could not imagine in 1935, that twin research would achieve such popularity nowadays. It still took more than 70 year after Lewis' remark to present a thesis that is completely focused on the genetic and environmental influences on Obsessive-Compulsive Symptoms (OCS) using extended twin designs.

See **Editorial** page 10

Daniël Sebastiaan van Grootheest, september 18th 2008, Amsterdam

OBSESSION

The genetic and environmental architecture of obsessive-compulsive symptoms

Daniël Sebastiaan van Grootheest

Reading committee
Prof. dr. A.J. van Balkom
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Prof. J.J. Hudziak
Dr. B.P.C. Koeleman
Dr. C.M. Middeldorp
Prof. D.L. Pauls

Paranimfs
Wessel-Jan Fijnvandraat
Tinca Polderman

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VRIJE UNIVERSITEIT

OBSESSION

The genetic and environmental architecture of obsessive-compulsive symptoms

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
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van de faculteit der Psychologie en Pedagogiek
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De Boelelaan 1105

door

Daniël Sebastiaan van Grootheest

geboren te Amsterdam

promotoren: prof.dr. D.I. Boomsma
prof.dr. A.T. Beekman

copromotor: dr. D.C. Cath

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CHAPTER 1

Aims and outline

van Grootheest, D. S.

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Aims and outline

"Dr. FE Pilkington has kindly let me see the record of another pair of probably identical twins who show striking similarity in their respective obsessional illnesses. But two or three pairs tell very little; it is a pity that twins are so rare" **by Aubrey Lewis (1935)**

Lewis could not imagine in 1935, that twin research would achieve such popularity nowadays. It still took more than 70 year after Lewis' remark to present a thesis that is completely focused on the genetic and environmental influences on Obsessive-Compulsive Symptoms (OCS) using extended twin designs.

In 2005, Kendler described four paradigms of psychiatric genetics, which are shown in table 1. Paradigm one, basic genetic epidemiology, has the goal to estimate the proportion of liability in a given population due to genetic and environmental differences between individuals. In case of genetic factors, this proportion is called heritability. Given a significant heritability, the goal of advanced genetic epidemiology, paradigm two, is to explore the nature and mode of action of these genetic risk factors, answering potential questions like: Do these genetic risk factors affect disease similarly in males and females? Do the actions of these risk factors change as a function of the developmental stage of the individual? Does the level of heritability for a disorder differ across populations? Paradigm three and four focus on gene finding and molecular genetics.

This thesis focuses on paradigms one and two within OCS using different assessment instruments in large twin samples. Two large samples came from the Netherlands Twin Register; one consisting of young twins (Bartels *et al.*, 2007) and a second sample consisting of adult twins and their family members (Boomsma *et al.*, 2006). Participants in both samples provided longitudinal data on OCS. The third sample came from the Virginia twin registry. The overall aim of this thesis is to explore the genetic and environmental architecture of OCS symptoms in the general population.

In *Part I* of this thesis we start with an overview and background of OCS and Obsessive-Compulsive Disease (OCD) (**chapter 2**). *Part I* continues with a review on all published twin studies on OCD and OC symptoms, starting with the first known published case of a MZ twin pair in 1929 (**chapter 3**).

In *Part II* of this thesis, heritability, assortative mating, and genetic and cultural transmission of OCS were examined. **Chapter 4** investigates the heritability of OCS, in a large sample of twins and sibs. Because of the large sample size we were able to take a closer look into the issue of sex-differences in the heritability of OCS. OCS was assessed with the YASR-OCS; a newly developed scale based on the 8 items of the CBCL-OCS in children (Nelson *et al.*, 2001; Hudziak *et al.*, 2006). **Chapter 5** evaluates causes of marital resemblance on OCS, and on two correlated traits, i.e. depressive and anxious symptoms in a population based twin-family sample. Resemblance between spouses can be due to phenotypic assortment, social homogamy and/or marital interaction. A significant degree of assortment, if it is due to phenotypic assortment, has consequences for the genetic architecture of a population. **Chapter 6** investigates the heritability of OCS, using the PI-R Abbreviated, a scale including 12 items of the Padua Inventory Revised (Van Oppen *et al.*, 1995). Data were derived from a large sample of twins, sibs and parents, and provided the opportunity to estimate genetic and environmental influences on OCS and the possible influence of cultural transmission, while controlling for assortative mating.

Part III is dedicated to genetic and environmental influences over time from child to adulthood. In **chapter 7**, longitudinal analyses in twin children are presented using both mother and father ratings in a combined multivariate multi-rater design. This chapter focuses on stability of OCS and examined the genetic and environmental influences on this stability. **Chapter 8** shows the results of cross sectional analyses at three different ages in a group of adolescents. **Chapter 9** focuses on longitudinal analyses in adults using 4 time-points and two different measurements.

Part IV of this thesis deals with the identification of environmental risk factors for OCS using a special twin design and offers in the second part a closer look at the heritability of symptom dimensions. In **chapter 10,** data from discordant and concordant monozygotic twins were used to investigate environmental factors that protect against or exacerbate obsessive-compulsive symptoms. **Chapter 11** shows results of a co-operation with the Virginia twin register and investigates the heritability of symptom dimensions in a sample of American female twins.

Finally, **chapter 12** summarizes and discusses the main findings of this thesis and evaluates directions for future research into the genetic epidemiology of OC symptoms.

Table 1. Four major paradigms of psychiatric genetics

Paradigm	Samples studied	Methods of inquiry	Scientific goals
1. Basic genetic epidemiology	Family, twin and adoption studies	Statistical	To quantify the degree of familial aggregation and/or heritability
2. Advanced genetic epidemiology	Family, twin and adoption studies	Statistical	To explore the nature and mode of action of genetic risk factors
3. Gene finding	High-density families, trios, case-control samples	Statistical	To determine the genomic location and identity of susceptibility genes
4. Molecular genetics	Individuals	Statistical	To identify critical DNA variants and trace the biological pathways from DNA to disorder

Adapted from Kendler (2005)

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PART I. INTRODUCTION TO OCD, OCS AND TWIN STUDIES

CHAPTER 2

Obsessive-compulsive symptoms and disease: an overview

This chapter is based on:

van Grootheest, D. S., van den Heuvel, O. A., Cath, D. C., van Oppen, P. & van Balkom, A. J.: Obsessieve-compulsieve stoornis. *Nederlands Tijdschrift voor Geneeskunde* (accepted).

Mataix-Cols, D., van den Heuvel, O. A., van Grootheest, D. S. & Heyman, I.: Obsessive–Compulsive Disorder, in: *The New Encyclopedia of Neuroscience* (NRSC), Larry Squire (ed), Elsevier Ltd., 2008.

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Obsessive-compulsive symptoms and disease: an overview

van Grootheest, D. S., van den Heuvel, O. A., Cath, D. C., van Oppen, P., van Balkom, A. J., Mataix-Cols, D., van den Heuvel, O. A., & Heyman, I.

ABSTRACT

This study provides a brief overview of the latest research on symptoms, epidemiology, neuro-anatomy, genetic and environmental factors, and management of Obsessive-Compulsive Disorder (OCD). OCD is a complex psychiatric disorder characterized by obsessions and/or compulsions. Obsessive-compulsive disorder has a relatively high prevalence of roughly 1% and is a highly disabling disease. The disorder is associated with shame, which causes long delays in accessing treatment. Differences between people in the liability to develop OCD are caused by a combination of genetic and environmental factors. Effective treatments exist, either pharmacotherapy or cognitive behavior therapy.

Obsessive-compulsive disorder (OCD) is a complex and heterogeneous psychiatric disorder characterized by obsessions and compulsions (also known as 'rituals'). Obsessions are unwanted ideas, images or impulses which repeatedly enter an individual's mind. Although recognized to be self-generated they are experienced as 'egodystonic' (out of character and distressing). Compulsions are repetitive behaviors or mental acts which are often intended to neutralize anxiety provoked by the obsessions (Figure 1). These rituals are often driven by rules that must be applied rigidly. In order to qualify for the diagnosis, the symptoms must be disabling.

Figure 1.

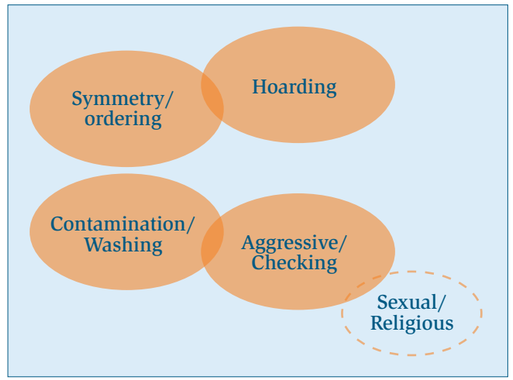
The OCD cycle. Obsessions are intrusive thoughts (ideas, images or impulses) which repeatedly enter an individual's mind against his/her will. These generate significant levels of anxiety and are difficult to dismiss. Compulsions or rituals are repetitive acts that are performed in an attempt to reduce the anxiety caused by the obsessions, but the relief is only temporary. Later in the course of OCD, rituals can become more automatic and increase, rather than reduce, the anxiety.

Figure adapted from Heyman et al. (2006)

SYMPTOMS

Although the core features of obsessions and compulsions appear to be remarkably consistent throughout the life span, in both sexes and in different cultures and races, the detailed content of these symptoms is varied. Two patients with OCD may present with completely non-overlapping symptom profiles. However, more commonly, patients experience multiple types of obsessions and compulsions. The most common types of obsessions and compulsions are listed in Table 1. These symptoms tend to group in predictable ways. Indeed, multiple factor and cluster-analytical studies (Leckman *et al.*, 2007) have identified at least 4 relatively independent and temporally stable symptom dimensions: 1) contamination obsessions and washing/cleaning compulsions, 2) aggressive, sexual and religious obsessions and related compulsions (often checking), 3) obsessions concerning a need for symmetry or exactness, ordering/arranging, repeating and counting compulsions, and 4) hoarding and collecting obsessions and compulsions (Figure 2).

Figure 2.



Schematic representation of the major symptom dimensions of OCD. Most studies consistently identified four symptom dimensions (continuous lines), while some others identified a fifth dimension consisting of sexual and religious obsessions (dashed line) but more research is needed to determine its validity. Note the overlap between these dimensions as mono-symptomatic patients are very rare.

Table 1. Most common types of obsessions and compulsions in a large sample of patients with OCD (n = 354)

Obsessions	N	%	Compulsions	N	%
Contamination	208	59	Cleaning	212	60
Aggressive	246	69	Checking	253	71
Sexual	68	19			
Religious	95	27			
Symmetry	159	45	Ordering	121	34
			Repeating	176	50
			Counting	125	35
Hoarding	77	22	Hoarding	73	21
Somatic	103	30			

Adapted from Mataix-Cols et al. (1999)

Aggressive and sexual obsessions in OCD must be differentiated from violent thoughts occurring in other disorders, such as urges to hurt people in psychopathy or abuse children in pedophilia. People with OCD fear that they might commit an offence but do not carry out the feared act and spend an excessive amount of time and energy resisting and controlling their behavior to avoid the risk of harm.

OCD often occurs together with other complicating conditions, such as depression or other anxiety disorders (Pigott *et al.*, 1994). Screening for, and treating these co-morbidities is an important part of the management of the disorder (see Table 2).

Table 2. Conditions commonly occurring with OCD

Condition	Frequency
Depression	50-60 %
Specific phobia	22 %
Social phobia	18 %
Eating disorder	17 %
Alcohol dependence	14 %
Panic disorder	12 %
Tourette's Disorder	7 %
Schizophrenia	14 %

Adapted from Piggott et al. (1994)

The majority of people with OCD of all ages understand the senseless nature of their repetitive, unwanted behaviors and intrusive, recurrent thoughts. This may lead to shame, reluctance to seek help, and poor recognition by health professionals. People with OCD have long delays in accessing effective treatments, with delays of 14 years on average, although younger patients had access to treatment sooner. Individuals with OCD frequently present to non-psychiatrists for treatment (Table 3) and psychiatric symptoms go undetected. There is a need for greater awareness of OCD in a range of non-psychiatric health care settings, and clinicians need to be confident about recognizing it.

EPIDEMIOLOGY

OCD can occur throughout the lifespan, with children as young as 6 or 7 presenting with the characteristic impairing symptoms. At the other end of the age-range, cases may present for the first time in old age. The majority of adults report the onset in childhood or adolescence. OCD can result in significant disability and the World Health Organization rates it as one of the top-twenty most disabling diseases. If untreated, OCD generally persists (Skoog & Skoog, 1999), yet there are effective, evidence-based psychological and pharmacological treatments.

Recent epidemiological studies report prevalence rates of about 1% in adults and in 0.25% of 5-15 year old children (Crino *et al.*, 2005; Heyman *et al.*, 2001), although earlier studies have suggested rates as high as 1-3% in adults (Karno *et al.*, 1988) and 1-2% in children and adolescents.

Table 3. Non-psychiatrists likely to see patients with OCD

Professional	Reason for consultation
General practitioner	Depression, anxiety
Dermatologist	Chapped hands, eczema, compulsive hair pulling
Cosmetic surgeon	Concerns about appearance
Oncologist	Fear of cancer
Genito-urinary specialist	Fear of HIV/AIDS
Neurologist	OCD associated with Tourette's Disorder
Obstetrician	OCD during pregnancy or puerperium
Gynaecologist	Fear of contamination, vaginal discomfort from douching

Adapted from Heyman et al. (2006)

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The causes of OCD are unknown but, like in most complex psychiatric disorders, are likely to stem from a combination of genetic, neurobiological, cognitive-behavioral and environmental factors.

THE FUNCTIONAL NEUROANATOMY OF OCD

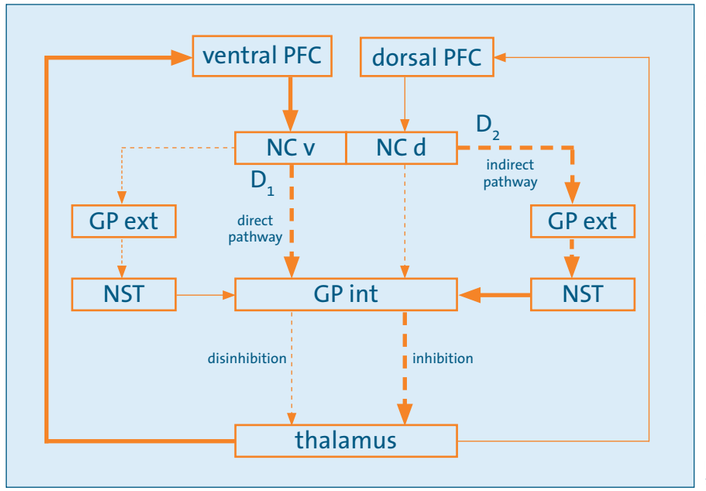
Current neurobiological theories of OCD suggest that specific frontal-subcortical circuits are involved in the symptoms and cognitive deficits associated with the disorder. These theories arose from various sources of evidence: the presence of OCD symptoms in some neurological conditions (Tourette's Syndrome, Huntington's Disease, Sydenham's Chorea) and other basal ganglia disorders (Laplane *et al.*, 1989), the emergence of OCD-like behaviors in patients with focal brain injury and the fact that surgical interventions that interrupt these frontal-subcortical circuits improve both mood and OCD symptoms. However, the strongest support for these models came from the advent of modern neuroimaging techniques, which provided a direct window into the OCD brain *in vivo*. Currently, the most widely accepted neuroanatomical model of OCD proposes the involvement of a direct and an indirect cortico-striato-thalamic pathway (Cummings, 1993; Saxena & Rauch, 2000). In the direct pathway, an excitatory glutamatergic signal projects to the striatum, sending an inhibitory GABA-ergic signal to the internal part of the globus pallidus. This results in a decreased inhibition (disinhibition) of the thalamus and thus an increased excitatory effect on the prefrontal cortex (Figure 3). In the indirect pathway, the striatum projects an inhibitory signal to the external part of the globus pallidus and the subthalamic nucleus, sending an excitatory signal to the internal part of the globus pallidus. The net effect is an increased inhibition of the thalamus and decreased excitation on the prefrontal cortex. It is hypothesized that the direct pathway functions as a self-reinforcing positive feedback loop and contributes to the initiation and continuation of behaviors, whereas the indirect pathway provides a mechanism of negative feedback which is important for the inhibition of behaviors and in switching between behaviors. Thus, an imbalance between these frontal-striatal circuits might mediate the symptoms of OCD: an excess tone in the direct relative to the indirect frontal-striatal circuit is hypothesized to result in enhanced activation of the orbitofrontal cortex, ventral striatum and medial-dorsal thalamus. Based on the positive therapeutic effects of selective serotonergic re-uptake inhibitors on OCD symptomatology and the inhibitory effect of serotonin on dopamine, it is suggested that failure of the serotonergic system results in decreased compensation of the dopaminergic influence on the frontal-striatal circuits. Dopamine (D) has a dual role on the balance between the direct and indirect frontal-striatal pathways. In the human brain D_1 receptor expression is prominent in the ventromedial (relative to dorsolateral) prefrontal cortex and ventral (relative to dorsal) striatum (Hurd *et al.*, 2001). Functionally, this dopaminergic differentiation implies a stronger D_1 influence on the *direct* pathway of the *ventromedial* frontal-striatal circuit and a stronger D_2 influence on the *indirect* pathway of the *dorsolateral* frontal-striatal circuit, resulting in a hyperactivated ventral and an inhibited dorsal frontal-striatal system (see Figure 3). This corresponds with the results of functional neuroimaging studies in OCD, showing increased activation of limbic and ventral frontal-striatal regions at rest and in response to disease-relevant information (Remijnse *et al.*, 2005) and decreased responsiveness of dorsal frontal-striatal regions during executive performance (van den Heuvel *et al.*, 2005)

INFLUENCE OF GENES AND ENVIRONMENT ON OCD

The influence of genetic factors in OCD has been suggested since the earliest descriptions of the disorder and a number of study designs have been employed to determine to what extent OCD is heritable. First, family studies have convincingly shown that OCD runs in families, that is, that first-degree relatives of OCD patients have an elevated risk of having OCD or sub-clinical obsessive-compulsive symptoms themselves (Pauls *et al.*, 1995; Nestadt *et al.*, 2000). These studies however do not allow disentangling whether this familiarity is due to genetic or environmental factors. For this purpose adoption or twin studies are needed. Adoption studies are generally rare, and to our knowledge no such studies have been published concerning OCD. An extensive overview of twin studies on OCS can be found in **chapter 2**.

Genetic linkage analysis provides a powerful approach to elucidate the underlying genetic factors in inherited disorders. Linkage studies are designed to determine whether a behavioral phenotype, such as psychiatric disorder or a dimensional trait, is physically linked to a genetic marker, a segment of DNA with a known physical location on a chromosome. Linkage studies on OCD are rare and have been performed in relatively small clinical samples. Two independent genome scans identified a region of chromosome 9p24 that had a suggestive linkage to early-onset OCD (Hanna *et al.*, 2002; Willour *et al.*, 2004). Recently, a large affected sib-pair sample from 219 families from the OCD Collaborative Genetics Study showed suggestive evidence for linkage in several regions including 1q, 3q, 6q, 7p, and 15q (Shugart *et al.*, 2006). The same group also found significant linkage to compulsive hoarding on chromosome 14 (Samuels

Figure 3. A widely-accepted frontal-striatal model of OCD.



PFC = prefrontal cortex;
NC d = dorsal part of caudate nucleus;
NC v = ventral part of caudate nucleus;
GP ext = external part of globus pallidus;
GP int = internal part of globus pallidus;
NST = subthalamic nucleus;
D1 = dopamine type 1,
D2 = dopamine type 2;

Dotted lines indicate inhibitory GABA-ergic projections;

Solid lines indicate excitatory glutamatergic projections.

Figure adapted from Mataix-Cols and van den Heuvel (2006).

et al., 2007). These findings strengthen the notion that OCD is a complex and heterogeneous disorder.

Association studies offer an alternative strategy for studying genetic factors and the aim is to demonstrate a significantly different distribution of candidate gene variants in affected (OCD) and unaffected (non-OCD) individuals. A large number of genetic association studies on OCD have been conducted in various populations, mainly investigating the possible contribution of genes to both the serotonergic and dopaminergic system. Unfortunately, the results of most association studies in OCD are inconsistent and inconclusive possibly due to a number of reasons including small sample sizes, the use of mixed populations, failure to account for multiple testing and the clinical heterogeneity of OCD. Recently, more statistically sound association studies have been conducted focusing on glutamatergic transmission. Two independent studies found an association of glutamate transporter gene SLC1A1, particularly in males (Arnold *et al.*, 2006; Dickel *et al.*, 2006). The encoding region for SLC1A1 lies on chromosome 9p24, a region where suggestive linkage was reported earlier. A meta-analysis of all published case-control data on catechol-O-methyltranferase (COMT) found evidence of an association between the met158 allele of (COMT) and OCD (Pooley *et al.*, 2007). The association was present in men but not in women. COMT has a role in cortical dopamine signaling and information processing. Another study reported an association between oligodendrocyte lineage transcripting factor 2 (OLIG2) and OCD (Stewart *et al.*, 2007), especially when Tourette's Disorder was absent. OLIG2 has an essential regulation role in the development of cells that produce white matter (myelin). The OLIG2 gene is also highly expressed in the brain regions implicated in OCD.

Although hereditary factors are important, a large proportion of the variation in OCS is mediated by environmental factors. Research into environmental factors of OCS is relatively scarce and the quality of the studies was moderate. There are indications of a variety of risk factors for OCS, including prenatal and perinatal complications, pregnancy and postpartum period, and severe life events, particularly sexual trauma (Miguel *et al.*, 2005). Much research is done to the relationship between infection and streptococcen OCS in children, the so-called Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) (Snider & Swedo, 2004). The controversy over this diagnosis and clinical consequences continues. Chapter ten further explores possible environmental factors of OCS.

MANAGEMENT OF OCD

Multiple randomized controlled trials (RCTs) have established the efficacy of both a form of psychotherapy called cognitive-behavior therapy (CBT) and certain medications which inhibit the synaptic reuptake of serotonin, i.e. the tricyclic antidepressant clomipramine and the more highly selective serotonin reuptake inhibitors (SSRI's) (van Balkom *et al.*, 1994). There is no evidence to support the efficacy of psychodynamic psychotherapy in OCD and its use is therefore not recommended.

In both adults and children, the specific CBT technique most strongly associated with good outcome in CBT studies is exposure and response prevention

(E/RP) (Abramowitz *et al.*, 2005). Briefly, the patient is encouraged to progressively face his/her feared situations (exposure), whilst refraining from performing his/her rituals (response prevention). Engaging the person with OCD by helping them design a graded programme of E/RP, and working collaboratively on easiest challenges first is essential. Careful education about mechanisms of anxiety, understanding that repeated exposure leads to reduced anxiety, as well as reduction in obsessions, is important for success. Practice is needed, as patients with OCD will have been reinforcing their behaviors by avoiding feared situations or carrying out rituals to deal with their fears for some time. It is often needed to involve the patients' family members in this process as many participate in (and thus help maintain) the patient's rituals.

All the SSRIs have been subject to large-scale clinical trials and have been found to be superior to placebo in both adults and children with OCD (Fineberg & Gale, 2005; Geller *et al.*, 2003). Dose-finding studies have only been carried out in adults. Higher doses of SSRIs are needed to effectively treat OCD, compared with depression. SSRIs have largely superseded clomipramine for treating OCD because of their lesser toxicity in over-dose and more favourable side-effect profile. This is especially important for children, where cardiac toxicity may be a risk. Head-to-head studies show equivalent efficacy and better tolerability for SSRI's relative to clomipramine (Zohar & Judge, 1996). Clomipramine remains a useful option, but is usually reserved for cases where trials of SSRIs have been ineffective.

There is some evidence supporting various medication strategies in resistant cases, including increasing the dose of the SSRI to the maximum tolerated, and switching to an alternative, as there may be idiosyncrasy in response. OCD does not respond to antipsychotics given as monotherapy. There is evidence from children and adults that adding low doses of first and second generation antipsychotics to SSRIs may benefit cases of resistant OCD and OCD with comorbid tics (Bloch *et al.*, 2006).

Several studies have shown that people with OCD continue to benefit from long-term medication but many patients relapse if medication is discontinued (Koran *et al.*, 2002). For at least some cases, therefore, treatment may need to be continued indefinitely. This is not the case with E/RP, where therapeutic gains are usually maintained long-term, although some boosting sessions may be required.

Despite the demonstrated efficacy of both CBT and SSRIs, up to 40% of cases fail to respond adequately to these treatments. Recent studies suggest that patients with hoarding symptoms may be particularly treatment resistant and new treatment approaches are being developed and tested for these patients (Saxena & Maidment, 2004).

Some centers offer neurosurgery (cingulotomy or anterior capsulotomy) for severe, treatment resistant OCD but, for obvious reasons, these treatments have not been evaluated in controlled trials and remain controversial.

More recently a reversible form of neurosurgery consisting of deep-brain stimulation of the anterior capsule/ventral striatum has been developed and tested in OCD with promising results but more large-scale controlled studies are needed (Greenberg *et al.*, 2006).

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CHAPTER 3

Twin studies on obsessive-compulsive disorder: a review

van Grootheest, D. S., Cath, D. C., Beekman, A. T. & Boomsma, D. I. (2005). Twin studies on obsessive-compulsive disorder: a review. *Twin Res Hum Genet*, 8, 450-458.

Twin studies on obsessive-compulsive disorder: a review

van Grootheest, D. S., Cath, D. C., Beekman, A. T. & Boomsma, D. I.

ABSTRACT

Genetic factors have historically been thought of as important in the development of obsessive-compulsive disorder (OCD). For the estimation of the relative importance of genetic and environmental factors, twin studies are an obvious approach. Twin studies of OCD have a long history, starting back in 1929. In this review, over 70 years of twin research of OCD is presented using four different approaches that represent the steps in the twin research of OCD from past to present. These steps include (1) case-studies of twins with OCD from the old literature, (2) twin studies of OCD using Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, (3) twin studies of OCD using a dimensional approach, comparing resemblances in monozygotic and dizygotic twins, and (4) twin studies of OCD using a dimensional approach, analyzing the data with Structural Equation Modeling. It is concluded that only the studies using the last method have convincingly shown that, in children, obsessive-compulsive symptoms are heritable with genetic influences in the range of 45% to 65%. In adults, studies are suggestive for a genetic influence on obsessive-compulsive symptoms, ranging from 27% to 47%, but a large twin study using a biometrical approach with continuous data is still needed to provide conclusive evidence. Strategies for future twin studies of OCD are discussed.

Obsessive-compulsive disorder (OCD) is a psychiatric disorder characterized by intrusive, unwanted thoughts, fears and images (obsessions) on the one hand and /or repetitive ritualized behavior or mental acts (compulsions) on the other hand (American Psychiatric Association, 1994). Compulsions are usually performed to relieve the anxiety and/or distress caused by the obsessions. The most frequent types of obsessions are fear of contamination, pathological doubt, somatic obsessions, need for symmetry, and sexual and aggressive obsessions. Well-known compulsions are checking, washing, counting, symmetry/precision and hoarding. Obsessive-compulsive (OC) symptoms are remarkably diverse and the clinical presentation can vary both within and across patients over time (Leckman *et al.*, 1997). Nowadays, many studies have provided strong evidence that OCD is not a unitary nosological entity, as suggested by the current concept of *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; DSM-IV-TR; American Psychiatric Association, 1994), but a clinically heterogeneous disorder (Miguel *et al.*, 2005). Patients experience a chronic or episodic course with exacerbations that can substantially impair social, occupational and academic functioning (Nestadt *et al.*, 2000). The lifetime prevalence of OCD is estimated between 0.7 and 2.5% (Horwath & Weissman, 2000). Family studies of OCD have suggested that OCD is familial (Grados *et al.*, 2003), which is not synonymous with heritable. Genetic-epidemiological methods to study the relative roles played by genes and environment in the etiology of OCD include twin and adoption studies. Adoption studies are generally rare and to our knowledge, no such studies have been published on OCD. Twin studies are based on the fact that monozygotic (MZ) twins are genetically identical, whilst dizygotic (DZ) twins share on average 50% of their segregating genes, which is similar to any nontwin siblings. If MZ twins resemble each other more than DZ twins, this is indicative for the importance of genetic influences on the trait under consideration. The influence of genetic factors has been suggested from the earliest descriptions of the disorder up until the present (Pauls & Alsobrook, 1999), but the twin studies literature on OCD has never been reviewed extensively, apart from some attention in book chapters (Billett *et al.*, 1998; Macdonald *et al.*, 1991). In this review, whether twin studies on OCD indeed suggest that OCD is a heritable disorder is addressed by giving an overview of all reported twin studies of OCD in the literature. We begin with case studies from the old literature and end with more recent twin studies using a model fitting approach. Finally, we draw conclusions about the heritability of OCD and discuss new strategies for future twin studies on OCD.

CASE STUDIES OF TWINS WITH OCD IN THE OLD LITERATURE, 1929 – 1965

In 1929, Lange published the first cases of twins with OCD in an article on the pathology of twins in psychiatry (Lange, 1929). This paper marked the beginning of twin studies on OCD. An overview of all published case studies of twins with OCD in the old literature, published between 1929 and 1965, is presented in Table 1.

Most studies of this era have failed to distinguish between OC neurosis and mixed neurosis, and showed a tendency to confuse OC neurosis with OC personality or obsessive traits (Hoaken & Schnurr, 1980). The history of OCD can partly explain this observation. In 1878, Westphal considered genetics to represent the most prominent etiological factor in OCD (Westphal, 1878). OCD was at that time a clearly defined psychiatric disorder, thought to be caused by organic factors such as a dysfunction of the autonomic nervous system. Largely based on the ideas Freud (1896), this view of OCD changed and by the second half of the twentieth century OCD was (1) separated into obsessive neurosis and obsessive personality disorder, (2) considered to be on a continuum, ranging from 'normal' neurotic behavior, through personality disorder to neurosis, which warranted psychotherapy, (3) thought to be largely caused by early traumatic experiences or environmental factors, (4) and governed by psychoanalytic theories (Denys, 2004). Clear definitions of obsessive neurosis or obsessive personality disorder did not exist and this is reflected in the different diagnostic information provided by the case studies. Most studies provide insufficient clinical data to verify a diagnosis of OCD, severely hampering judgment on whether the subjects would meet current standardized diagnostic criteria (Billett *et al.*, 1998). Moreover, comparison of the case studies is difficult due to differences in diagnostic criteria between studies. Furthermore, there seemed to be a tendency to publish MZ and concordant twins, introducing reporting bias. This bias is caused by collecting twins in an unsystematic way, which tends to favor MZ and concordant pairs (Clifford *et al.*, 1984). Another problem with case studies was mentioned by Lewis (1935) who wrote that 'a striking concordance in one or two pairs of MZ twins proves nothing: one needs a series and control group of fraternal twins'. It is interesting however that Woodruff and Pitts (1964) regarded even one set of MZ twins concordant for obsessional illness as important, stating that it was statistically improbable for MZ twins to be concordant in the absence of common determinants. This conclusion was based on their frequently cited calculation of the prevalence of OCD of 0.05% in the general population (Woodruff & Pitts, 1964). They wrote that one in 132 live births are MZ twins and calculated that the chance of finding a pair of MZ adult twins where both had OCD would be one in 600 million if the disorder would arise independently in each co-twin and was not due to some combination of shared genetic or environmental factors.

The twin rule of pathology, that is any heritable disease will be more concordant in identical twins than in nonidentical twins, was already formulated in 1924 (Siemens). But around 1960 the debate continued as to which conclusions could be drawn from the finding of a marked increased concordance of MZ compared to DZ twins in schizophrenia (Parker, 1964). Besides the conclusion that a genetic predisposition could exist, an exclusive environmental basis for this consistent finding was also proposed (Jackson, 1960). This environmental basis could be caused by close identification or by confusion of ego identity, which was suggested to occur in MZ twins (Jackson, 1960). Rosenthal (1960) had already shown that the second factor could not be held responsible, as twins in general would then be expected

Table 1. Case studies of twins with OCD in the old literature

Study	No. of twin pairs	Zygosity determination supported	MZ C/D	DZ C/D	Diagnostic information
Lange (1929)	3	No	1/2		'Obsessional symptoms' ; One MZ twin with brain damage.
Le Gras (1932; 1933)	1	No	1/0		'Hysteria with Obsessional symptoms'
Lewis (1935)	3	No	2/1		'Obsessional illness'; One pair with OCP.
Tarozzi (1939)	1	No	1/0		'Psychoneurosis with obsessional ideas'
Rüdin (1953)	1	No		0/1	'Obsessional neurosis'
Tienari (1963)	11	No	10/1		'Phobic or obsessional neurosis' Mix of OC features, traits and syndromes.
Parker (1964)	2	Yes	0/2		'Obsessional neurosis'
Woodruff & Pitts (1964)	1	Yes	1/0		'Obsessional behavior'
Inouye (1965; Ihda, 1965)	14	No	8/2	1/3	'Obsessive-compulsive reaction'; One case likely Tourette's syndrome.

MZ, monozygotic twins; DZ, dizygotic twins; C/D, concordant/discordant; OCP, obsessive-compulsive personality disorder; OC, obsessive-compulsive

to have a higher incidence of schizophrenia than the general population, which is not the case. Parker (1964) described two MZ twins discordant for OCD, attempting to illustrate with these cases that marked identification can still occur without both twins developing symptoms of neurotic illness, throwing doubt on the validity of this purely environmental theory.

A further limitation of the old literature is the lack of any procedural blind to obtain diagnostic information or establish diagnoses. Knowledge of an index case's status while evaluating the co-twin or vice versa is an unacceptable source of bias (Pauls & Alsobrook, 1999). Finally, in many cases the method of zygosity determination is unclear or there is lack of information to definitively establish monozygosity. With these limitations in mind, no conclusions on the heritability of OCD can be drawn from this literature.

TWIN STUDIES OF OCD MEETING DSM CRITERIA

The development of the DSM-III (3rd ed.; American Psychiatric Association, 1980) meant a new step forward in psychiatric research. Disorders in DSM-III have been defined in terms of syndromes, that is, symptoms that are observed in clinical populations to covary together in individuals. The major advantage of adopting a descriptive classification was its improved reliability over prior classification systems using nonoperationalized definitions of disorders. From the outset, however, it was recognized that the primary strength of this descriptive approach was its ability to improve communication among clinicians and researchers, not its established validity (Kupfer *et al.*, 2002).

Table 2 shows several case studies and four larger epidemiological twin studies on OCD, meeting DSM-III or DSM-III-R (3rd ed., rev.; American Psychiatric Association, 1987) criteria. The standardization of the diagnosis and higher reliability of the zygosity determination diminish some limitations of the case studies described above. Although case studies of twins with OCD can hardly solve the question about heritability, they can inspire researchers by generating new hypotheses, which can be a starting point for subsequent research. For example, McKeon *et al.* (1984) described four cases of OC neurosis following head injury, one from a discordant MZ twin pair. The twin is a 23-year-old Ugandan immigrant who started having OC symptoms after he was knocked down by a car and had been unconscious for 10 days. His rituals involved repeated checking of his clothing, brushing his teeth for more than an hour at a time and taking extensive precautions to avoid contamination in the bathroom. His early development had been normal and closely similar to that of his co-twin, who had at no period in his development exhibited OC symptoms. However, following the head jury, the twins' behavior became clearly discordant from his brothers. The authors conclude that head injury is a probable contributor to the development of OC neurosis in some cases.

Four epidemiologic studies were published that will be described more extensively. Carey and Gottesman (1981) selected 30 twin pairs, 15 MZ and 15 DZ, from the Maudsley Twin Register, which represents a consecutive series of patients who were admitted to the Maudsley or Bethlem hospitals between 1948 and 1979. All probands reported unequivocal obsessional symptoms according to DSM-III criteria. The diagnosis may have been secondary to another diagnosis, so the results apply to obsessional symptoms that occurred both on their own and in addition to other psychiatric disorders. Concordance rates for 'obsessive symptoms or features with or without treatment' were 87% for MZ pairs and 47% for DZ pairs. Concordance rates for an 'episode of psychiatric or GP treatment involving obsessional symptoms' were 33% for MZ pairs and 7% (one twin pair) for DZ pairs.

Torgersen (1983) investigated genetic factors in the determination of six anxiety disorders in a study of 32 MZ and 53 DZ adult same-sex twin pairs from Norway. The sample consisted of twins born between 1910 and 1955 who were admitted for the treatment of neurotic or borderline psychotic disorder prior to 1977. Each twin was diagnosed according to DSM-III criteria. Of the 85 probands, 12 twins, 3 MZ and 9 DZ, had an OCD, but no co-twins with OCD were found. Although no twins were found to be concordant for any of the other DSM anxiety disorders either, the author examined concordance rates in the larger context of an 'anxiety spectrum' (Pauls & Alsobrook, 1999). When the sexes were combined, the concordance for anxiety disorders in the proband group labeled 'all anxiety disorders without General Anxiety Disorder (GAD)' was 45% in MZ pairs to 15% in DZ pairs. The author concludes that genetic factors appear to influence the development of anxiety disorders in general, with the exception of GAD.

Andrews *et al.* (1990) administered structured psychiatric interviews on DSM-III criteria, the Composite International Diagnostic Interview (CIDI), to 186 MZ and 260 DZ twin pairs, culled from the Australian Twin Registry. Lifetime diagnoses for major depressive disorder, dysthymia, GAD, OCD, panic disorder, social phobia and agoraphobia with panic were obtained. In total, 48 twins with a diagnosis of OCD were reported, but no concordant twin pairs with OCD were found. Although there was a genetic contribution to neuroticism and to symptoms of depression and anxiety, no inheritance of any specific disorders was found.

Skre *et al.* (1993) performed a twin study of DSM-III-R anxiety disorders in 81 same-sex twin pairs. The sample of twin probands consisted of twins with nonpsychotic disorders and was ascertained from several subsamples of twins in Norway. One subsample overlapped with the sample used in the study of Torgersen (Torgersen, 1983). In the anxiety disorder proband group containing 20 MZ and 29 DZ twins, 3 MZ twins and 2 DZ twins were found to have OCD. In the co-twin group of the anxiety probands, 2 MZ twins with OCD were found but it is not clear in the article if these are concordant MZ twins or not. In the co-twins of the comparison group with probands having no anxiety disorder at all, another DZ twin with OCD was found. The authors conclude that their results do not contribute to a clarification of the etiology of OCD.

Several important aspects may limit the interpretation of these epidemiologic studies. Although the use of DSM-III or DSM-III-R criteria reduces the risk of false-positive diagnoses, the failure to use separate interviewers for each member of a twin pair with each interviewer blind to the zygosity status of the pair introduces a large potential for inadvertent bias in the detection of illness (Pauls & Alsobrook, 1999). Torgersen (1983) and Andrews *et al.* (1990) combined different diagnostic categories to determine concordance rates. Although both groups of investigators argue that the results support the notion that there are common genetic factors for at least some anxiety disorders, by combining across diagnoses, both groups could have been capitalizing on chance (Pauls & Alsobrook, 1999). Lastly, in population-based samples, the low prevalence of DSM-diagnosed OCD generally will lead to low statistical power to ascribe the familial clustering of OCD to either shared genes or shared environment.

TWIN STUDIES OF OCD USING A DIMENSIONAL APPROACH, COMPARING RESEMBLANCES IN MZ AND DZ TWINS

The classical twin method compares phenotypic resemblances between MZ and DZ twins. Comparing the resemblance of MZ twins for a trait or disease with the resemblance of DZ twins offers an estimate of the extent to which genetic variation determines phenotypic variation of that trait: the heritability (h^2; Boomsma *et al.*, 2002). The classical twin method allows the use of categorical data like diagnoses but also continuously distributed traits, such as obsessional trait or symptom scores in twins. Macdonald *et al.* (1991) recommended that instead of relating diagnoses to thresholds on an underlying liability distribution, we should aim for measures that are more direct indices of this liability distribution and hence examine the genetic and environmental basis of individual differences in vulnerability to develop clinically significant OCD.

Table 2. Twin studies of OCD meeting DSM-III or DSM-III-R criteria

Study	No. of twin pairs	MZ C/D	DZ C/D	Diagnostic information
Marks et al. (1969)	1	1/0		
Tarsh (1978)	1		1/0	Both twins improved after leucotomy
Hoaken & Schurr (1980)	1	0/1		
McGuffin & Mawson (1980)	2	2/0		
Carey & Gottesman (1981)	30	13/2	7/8	
Torgersen (1983)	12	0/3	0/9	
McKeon et al. (1984)	1	0/1		OCD after head injury
Mahgroub et al. (1988)	1	1/0		First-born twin has also epilepsy. Second-born twin minor OC symptoms
Kim et al. (1990)	1	1/0		
Andrews et al. (1990)	48	0/18	0/30	
Lewis et al. (1991)	3	3/0		All three twin pairs disconcordant for schizophrenia/ schizoaffective disorder
Cryan et al. (1992)	1	1/0		Both concordant for OCD and Paraphilia. Twin part of triplet
Skre et al. (1993)	8	5 *	0/3	

MZ, monozygotic twins; DZ, dizygotic twins C/D; concordant/discordant; OC, obsessive-compulsive
*concordance not clear

OCD is in this case viewed as the equivalent of extreme sores on symptom or trait measures. Such a dimensional approach removes the problem of scarcity of twins with the full disease and also removes the need for population-based prevalence rates for comparison.

Young *et al.* (1971) were the first researchers to apply a dimensional approach to OCD, using OC symptoms (Table 3). They conducted a small study of 17 pairs of identical male twins and 15 pairs of fraternal twins to examine the inheritance of neurotic traits. The 32 twin pairs completed the Middlesex Hospital Questionnaire, which contains a brief obsessional traits and symptoms subscale. Comparison of the intraclass correlations between the two twin series did not reveal a significant difference on the obsessional subscale score.

Table 3. Twin studies of OCD using a dimensional approach, comparing resemblances in MZ and DZ twins

Study	No. of twin pairs	Sample characteristics	Diagnostic information
Young et al. (1971)	32	Only men, cross sectional data	Obsessional traits and symptoms according to a subscale of the Middlesex Hospital Questionnaire
Torgersen (1980)	99	Men and women, cross sectional data	Obsessional traits according to the Lazar et al. questionnaire
Clifford et al. (1984)	419	Men and women, cross sectional data	OC-symptoms according to the Leyton Obsessional Inventory

OC, obsessive-compulsive

Torgersen (1980) examined 99 same-sex pairs of twins, 22 MZ female, 28 MZ male, 27 DZ female and 22 DZ male twin pairs. Eleven pairs were selected on the basis of hospitalization of one of the twins for neurotic problems. The remaining pairs were derived from the folk register of two cities to represent twin pairs from the general population. Torgersen compared intrapair variations of an obsessive personality factor, but did not find a significant difference between the MZ and DZ twins. The heritability of the obsessive scale was .18 for men and .23 for women. Torgersen hypothesized that in our society, a possible genetic core may perhaps be masked by the overwhelming environmental influences. It is difficult to evaluate the significance of these findings because of low statistical power and the biased ascertainment of twins. Furthermore, the obsessional scale used measured persistent personality traits rather than state dependent repetitive behavior (Macdonald *et al.*, 1991).

The paper of Clifford *et al.* (1984) marked the beginning of research on quantitative traits in relatively large samples of twins from the normal population, measuring OCD using standardized instruments and with a promising dimensional approach. Clifford *et al.* were well aware of the disadvantages of case studies and stated that 'if obsessional neurosis is regarded as a distinct disease entity qualitatively different from normal behavior, then it is almost impossible to devise ways of examining any possible etiological role for heredity. However, a more contemporary view of the neuroses considers them as conditions to which individuals towards the extreme ends of normally distributed symptom or trait dimensions are especially prone. A sample of 419 twin participated, with a bias towards female and MZ twins. Obsessionality was measured using a 42-item version of the Leyton Obsessional Inventory (Cooper, 1970). It contained 10 items of the trait scale and 32 items of the symptom scale. The heritability estimates for obsessional traits and symptoms were 44% and 47% respectively. No effect of common environment was found, thus unique environment explained the remaining variation. Multivariate analysis revealed two genetic factors of obsessionality, one factor related to a general trait of neuroticism and most strongly related to incompleteness and gloomy thoughts. The second genetic factor was related to checking and cleanliness. Finally considerable hereditary variation appeared to be specific to each of the four factors

TWIN STUDIES OF OCD USING A DIMENSIONAL APPROACH, ANALYZING THE DATA WITH STRUCTURAL EQUATION MODELING

The quantitative traits that have been assessed in MZ and DZ twins have traditionally been analyzed using analysis of variance and intraclass correlations to summarize twin resemblances (Boomsma *et al.*, 2002). However, this approach cannot accommodate the effect of sex on variances and covariance within and between twin pairs, nor can results easily be extended to multivariate and longitudinal data. Structural Equation Modeling (SEM), also known as covariance modeling, is a more general alternative approach, in which genotypic and environmental effects are modeled as the contribution of unmeasured (latent) variables to the potentially multivariate phenotypic differences between individuals (Neale & Cardon, 1992).

Jonnal *et al.* (2000) used this approach in a twin study of OCD, examining 527 pairs of female twins using 20-items of the Padua Inventory (Sanavio, 1988; Table 4).

Table 4. Twin studies of OCD using a dimensional approach, analyzing the data with structural equation modeling

Study	No. of twin pairs	Sample characteristics	Diagnostic information
Jonnal et al. (2000)	527	Only women, Cross-sectional data	OC-symptoms according to 20 items of the Padua-Inventory
Eley et al. (2003)	4564	Children aged 4 years, Cross-sectional data	OC behavior according to a 4 item OC scale
Hudziak et al. (2004)	4246	Children aged 7, 10 and 12 years, longitudinal data.	OC-symptoms according to a 8-item OC scale contained in the Child Behavior Checklist.

OC, obsessive-compulsive

The sample consisted of 334 female MZ twins and 193 pairs of DZ twins from the Virginia Twin Registry. A principal component analysis on the 20 items showed a two-factor solution which divided the items into a compulsiveness factor and an obsessiveness factor. By using SEM, the best-fit model suggested heritabilities of 33% and 26% for obsessiveness and compulsiveness respectively. Unique environmental effects accounted for 67% and 74% of the variance. The correlation between additive genetic effects on obsessiveness and compulsiveness was .53. The main conclusion was that self-report symptoms of obsessions and compulsions in women in the general population are moderately heritable and partly due to the same genetic risk factors. They also tested the equal environment assumption (EEA). Twin studies assume that MZ and DZ twin pairs are equally correlated for the exposure to environmental factors of etiologic relevance to the trait under study. No environmental effects that could be affecting the heritability were found and it was concluded that the EEA was not violated. Jonnal *et al.* (2000) noted three potentially important methodological limitations. First, they only selected a subset of items from the Padua Inventory, reducing the ability to detect a more complex and stable structure and increasing error variance. In a cross-sectional design, error variance cannot be distinguished from individual-specific environment with an underestimation of the impact of genetic factors as a result. Second, the study included only women, so conclusions cannot be generalized to men. Third, the data exhibited a pronounced right skew, although similar heritability estimates were produced after correction.

Eley *et al.* (2003) examined the phenotypic differentiation and genetics of mother-reported anxiety-related behaviors in 4564 4-year-old twin pairs from a population-based twin study, the Twins Early Development Study. Parents completed a 16-item questionnaire on anxiety-related behaviors in young children. The items were selected to assess five dimensions, including OC behavior (four items). For OC behavior there was substantial genetic influence with a heritability estimate of 65% and a 35% estimate of nonshared environment. Small negative sibling interaction effects were found, indicating rater-contrast or sibling competition effects.

Recently Hudziak *et al.* (2004) examined 4246 twin pairs of the Netherlands Twin Register (NTR) and 1461 twin pairs from the Missouri Twin Study Sample (MOTWIN). The 4246 twin pairs of the NTR were aged 7 years, of whom 2841 were reexamined at age 10 and 1562 were reexamined at age 12. The participants of MOTWIN were a mixed-age group with an average age of 9 years. An 8-item Obsessive-Compulsive Scale (OCS) was used from the Child Behavior Checklist (CBCL; Achenbach, 1991). The scale was validated in a clinical sample of children with OCD based on DSM-IV criteria and showed adequate predictive value (Nelson *et al.*, 2001). Across age groups and cultures, the best fitting model indicated additive genetic influences of the CBCL OCS score between 45% and 61%, and unique environmental influences between 42% and 55%. Only the NTR sample aged 12 years showed shared environmental influences of 16%. Minor sex differences were seen in the mixed-age MOTWIN twins only. No evidence of dominance, sibling interaction, or rater-contrast effects was seen.

Because of the age of the study sample, both Eley *et al.* (2003) and Hudziak *et al.* (2004) had to rely on parent reports, which may be influenced by characteristics of the rater.

CONCLUSION

Although the first twin report was written on OCD in 1929, it was not until 50 years later that Clifford *et al.* (1984) suggested genetic effects on obsessional symptoms, particularly cleanliness and checking. This study showed a first clear indication for the heritability of OC symptoms, moreover displaying a foreseeing notion of the multidimensionality of OCD. Although earlier twin studies have sometimes suggested the role of genes in OCD, several limitations diminish the utility of this literature (Billett *et al.*, 1998; Black, 1974). Therefore both Macdonald *et al.* (1991) and Pauls and Alsobrook (1999) concluded that due to the absence of twin studies to replicate the Clifford *et al.* findings, the effect size of genetic influences on OCD was still undetermined.

Strikingly, 15 years lapsed since the publications of Clifford *et al.* before a second informative twin study on the heritability of OC symptomatology was published in female twins (Jonnal *et al.*, 2000). However, in their review and meta-analysis of the genetic epidemiology of anxiety disorders, Hettema *et al.* (2001) could not find twin studies on OCD that met their inclusion criteria. These criteria for twin studies were the use of operationalized diagnostic criteria and systematic ascertainment of probands. Only recently is methodologically sound research emerging, investigating the contribution of disease-specific and common underlying genetic make-up in the occurrence of OC symptoms in children (Eley *et al.*, 2003; Hudziak *et al.*, 2004).

In conclusion, twin studies of children provide support for the hypothesis that genetic factors play a significant role in OC manifestation. Twin studies of adults are indicative, but a large twin study using a biometrical approach with continuous data is needed to provide conclusive evidence.

FUTURE OF TWIN STUDIES AND OCD

Recent research on OCD has made clear that OCD appears to encompass a heterogeneous phenotype with at least four symptom dimensions (Mataix-Cols *et al.*, 2005). This heterogeneity may obscure the findings of clinical, natural history and treatment response studies and complicates the search for vulnerability genes (Miguel *et al.*, 2005). A better description of clinical phenotypes should facilitate genetic studies. In fact, dissecting the phenotype into less complex components may be an important tool in the identification of susceptibility genes in OCD. Miguel *et al.* (2005) suggested three possible approaches. First, narrowing the phenotype to identify categorically defined homogeneous and mutually exclusive subtypes of OCD like tic-related OCD or early onset OCD. Second, considering OC symptom dimensions as quantitative components of the more complex OCD phenotype, like cleaning or hoarding. Third, broadening the phenotype to include other etiologically related conditions, for example generalized anxiety disorders and OCD spectrum disorders (Hollander, 1993). A combined dimensional approach within distinctive subgroups is proposed as probably the most effective in helping to identify the heritable components of OCD. What can the twin design contribute to this approach?

The first step would be to replicate factor-analyzed OC-symptom dimensions in an epidemiological twin sample and to calculate heritabilities per symptom dimension. Parameters like tic-relatedness or age at onset can be included. The twins who fall in a certain dimension and/or subgroup with high heritability can be further examined in linkage studies. By using this approach the identification of susceptibility genes for OCD may come closer to reality. This approach still uses the MZ-DZ comparison to estimate the contributions of genetic and environmental effects to phenotypic variance, in this case an OCD dimension. Extending the MZ-DZ design to include the testing of parents, siblings, spouses and offspring offers the opportunity to assess the presence of cultural transmission, genotype X environment covariance, nonrandom mating and social interactions within and between generations (Truett *et al.*, 1994). Extended twin designs also enable assessment of the effect of age difference on heritability and assessment of differential gene expression as a function of age (Boomsma *et al.*, 2002). One can imagine that partially different genes influence OC symptom levels and dimensions at different ages. This may be important information for gene-finding studies, as there may be a limited time period during which various genes engaged in OC symptoms over the course of an individual's life can be detected.

One step further is the use of multivariate analyses in which the causes of association and co-morbidity between traits and genotype X environment interaction can be investigated (Boomsma *et al.*, 2002). Multivariate twins studies enable research on questions such as: does a certain OC symptom dimension increase the risk for another symptom dimension, or is there a common genetic vulnerability for both? In line with the third approach mentioned by Miguel *et al.* (2005), it might be fruitful to analyze the causes of co-morbidity in a multivariate twin design and establish the extent to which symptom dimensions that cluster share a common genetic basis.

Another step to enhance the discriminative capacity of linkage and association studies in understanding the genetic basis of OCD would be to identify endophenotypes associated with OCD (Miguel *et al.*, 2005). Endophenotypes are defined as measurable components unseen by the unaided eye along the pathway between disease and distal genotype (Gottesman & Gould, 2003). At this moment, structural and functional neuroimaging studies are most promising to identify endophenotypes for OCD. If suitable endophenotypes can be found, multivariate analyses are needed for the simultaneous modeling of OC symptoms/dimensions and endophenotypes to determine their common genetic etiology.

If, at last, genes can be found for OCD, quantitative and molecular genetic methodology will be applied simultaneously to patients and controls, sib pairs, twins, and so on to study the effects of genes in different environments or the impact of different therapeutic interventions in different genotypic groups (Sham, 2003). After more than 70 years of twin studies on OCD, a new chapter of twin studies on OCD is just beginning.

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PART II. HERITABILITY, ASSORTATIVE MATING AND CULTURAL TRANSMISSION OF OCS

CHAPTER 4

Genetic and environmental influences on OC symptoms in adults: a population based twin-family study

van Grootheest, D. S., Cath, D. C., Beekman, A. T. & Boomsma, D. I. (2007). Genetic and environmental influences on obsessive-compulsive symptoms in adults: a population-based twin-family study. *Psychol Med*, 37, 1635-1644.

Genetic and environmental influences on OC symptoms in adults: a population based twin-family study

van Grootheest, D. S., Cath, D. C., Beekman, A. T. & Boomsma, D. I.

ABSTRACT

Background The contribution of genetic factors to OC symptoms has not been examined using a large population based sample of adults. Furthermore, the extent to which there are qualitative and quantitative differences in genetic architecture between men and women with OC symptoms has not been elucidated.

Methods We obtained the Young Adult Self Report Obsessive-Compulsive Scale (YASR-OCS) from a group of 5893 mono -and dizygotic twins, and 1304 additional siblings from the population-based Netherlands Twin Register. Structural Equation Modeling was used to decompose the variation in obsessive-compulsive (OC) behavior into genetic and environmental components and analyze quantitative and qualitative sex differences.

Results Familial resemblance was the same for DZ twins and non-twin siblings, which means that there was no evidence for a special twin environment. The same genetic risk factors for OC behavior were expressed in men and women. Depending on the choice of fit-index we found small (39% for men and 50% for women) or no sex-differences (47% for both men and women) in heritability. The remaining variance in liability was due to individual-specific environment.

Conclusions OC behaviour showed a moderate heritability. At most, small quantitative sex differences were found in the genetic architecture of OC behaviour, and no qualitative sex differences.

Historically, family-genetic studies have strongly suggested genetic factors to be important in the development of obsessive-compulsive disorder (OCD) (Black *et al.*, 1992; Pauls *et al.*, 1995; Nestadt *et al.*, 2000b). For the determination of the relative importance of genetic and environmental factors, twin studies are an obvious choice. Twin studies of OCD have a long history, starting back in 1929 (Lange) and evolving from single case reports to large epidemiological studies (van Grootheest *et al.*, 2005). A paper by Clifford *et al.* (1984) marked the beginning of research on quantitative obsessional-compulsive (OC) traits in relatively large twin samples from the normal population, measuring OCD with standardized instruments. Clifford *et al.* (1984) analyzed the 42-item version of the Leyton Obsessional Inventory (Cooper, 1970), obtained in 419 adult male and female twin pairs. The heritability of the obsessive symptoms was estimated at 47%. Surprisingly, since then only one twin study on OC symptoms in adults has been published. Jonnal *et al.* (2000) examined data from 527 pairs of female MZ and DZ twins from the Virginia Twin Registry, using 20 items of the Padua Inventory (PI) (Sanavio, 1988). The best model for these data suggested heritabilities of 33% and 26% for obsessiveness and compulsiveness respectively.

In children, a large twin study on OC behavior, assessed by the Child behavior Checklist Obsessive-Compulsive Scale (CBCL-OCS), was conducted in an American and Dutch twin sample (Hudziak *et al.*, 2004). OC behavior was assessed at ages 7, 10 and 12 years and showed a heritability of approximately 55%. Significant sex differences in heritabilities were only seen in the USA sample. Van Grootheest *et al.* (2007) found that stability of OC behavior in children, using the CBCL-OCS at ages 7, 10 and 12 years in a longitudinal design, was influenced by genes and both shared and non-shared environmental factors. Recently, Bolton *et al* (2007) examined 6-year old twins on OC symptoms. The effect of familial aggregation was estimated as 47% for sub-threshold OCD, but the study missed power to distinguish shared environment from genetic factors.

In conclusion, twin studies are suggestive of genes to be important for variation in OC behavior in children. For adults, a large twin study in males and females using a biometrical approach with continuous data is needed to provide more conclusive evidence and explore additional questions (van Grootheest *et al.*, 2005). Especially the impact of sex on the transmission of obsessive-compulsive disorder in adults is unknown. Sex effects can either be quantitative in nature, i.e. sex differences in magnitude of heritability, or qualitative, i.e. whether the genetic risk factors for OC symptoms in men and women are the same. Knowledge about sex effects in genetic risk for OCD is important because some literature on sex differences, although not always consistent, in OCD exists. Clinical studies of OCD showed that males are more likely to have a childhood onset, have a more chronic course of disease and show OC symptoms which are associated with a distinct pattern of comorbid psychopathology (Geller *et al.*, 1998; Eichstedt & Arnold, 2001). A variety of association studies have produced variable evidence for association in one sex or another (Camarena *et al.*, 2001; Enoch *et al.*, 2001; Alsobrook *et al.*, 2002; Lochner *et al.*, 2004; Hemmings & Stein, 2006). Segregation analyses suggest that the inheritance of OCD could be affected by sex effects (Nestadt *et al.*, 2000a; Hanna *et al.*, 2005).

The aim of this study is to determine the genetic and environmental contributions to obsessive-compulsive symptoms in adults by using a large sample of unselected twins and siblings. To maximize the statistical power and to test if results generalize to non-twins, the classical twin design was extended by including siblings (Posthuma & Boomsma, 2000; Stoel *et al.*, 2006). OC symptoms were assessed using the adult version of the CBCL-OCS, the Young Adult Self Report Obsessive Compulsive Scale (YASR-OCS). The criterion validity of the YASR-OCS was tested with Receiver Operating Characteristic (ROC) analyses among three different groups: an OCD group, a psychiatric control group and a population control group. We sought answers to the following questions:

1. What are the psychometric properties of the YASR-OCS?
2. Can results from our study be generalized to non-twins?
3. What role do genetic and environmental factors play in the etiology of OC symptoms?
4. Are genetic and environmental risk factors for OC symptoms of similar importance in males and females?
5. Are the genetic risk factors for OC symptoms in men the same as in women?

METHODS

Subjects

This study is part of a longitudinal survey study in twin families registered with the Netherlands Twin Register (Boomsma *et al.*, 2002; Boomsma *et al.*, 2006). Since 1991, every two to three years twins and their families have received a survey by mail containing questionnaires about health, personality and lifestyle. Participants in this study were adolescent and adult twins (mean age: 22.4, SD: 8.3) and their siblings (mean age: 28.0, SD: 11.0). Data were available for twins who participated in survey 1991, 1995 and 1997 and for siblings who participated in the survey of 1997. The data from these 3 surveys were used to create a large cross-sectional data set. We added, when possible, two additional sibs to each twin family. First, data of twin pairs and their siblings from the 1997 survey were used. If no twin data were available in 1997, then data of twin pairs collected in 1995 or 1991 were used. Half sibs, adoptive sibs and triplets were excluded. The resulting sample consists of 5893 twins: 3360 females and 2533 males from 3069 families. We were able to include 1304 additional non-twin siblings, 713 sisters and 591 brothers. A non-twin sibling can form a (twin-)sibling pair with one twin-brother or sister, and a (twin-)sibling pair with his other twin brother or sister. In the case of two siblings, the siblings form a sibling pair by themselves. These non-twin siblings increased the number of sibling pairs with 2773. As a consequence of the inclusion of additional siblings the monozygotic (MZ)-pair to dizygotic (DZ)-pair ratio decreased from .75 (792/1058) to .21 (792/3831). It has been shown that a MZ to DZ ratio of about 1 to 4 is optimal in terms of statistical power (Nance & Neale, 1989). Table 1 provides information on the twin/sibling composition and sex distribution of the participating families for each zygosity group. Zygosity of the twins was determined using items about physical similarity and the frequency of confusion of the twins by family and strangers. On 869 same sex twin pairs, information on their zygosity was available from DNA polymorphisms. The agreement between zygosity diagnoses of the questionnaire and DNA data was 98% (Willemsen *et al.*, 2005).

Receiver Operating Characteristic (ROC) analyses were conducted among three different groups: an OCD group, a psychiatric control group and a population control group. Data on patients with OCD were derived from the outpatient anxiety clinic of GGZ Buitenamstel, a specialized centre for anxiety disorders in Amsterdam. All participants who presented themselves for diagnosis and/or treatment of OCD between August 2004 and September 2005 were invited for a longitudinal study of OCD. In total, 68 participants, 22 men and 46 women with a mean age of 36.8 (SD = 10.2), were diagnosed by trained psychiatric residents using the Structured Clinical Interview of DSM-IV (SCID-I), 4th edition (First *et al.*, 1996). A group of 66 psychiatric control participants without OCD, consisting of 16 men and 50 women with a mean age 36.6 (SD = 9.8), was obtained from an adult sample of the Netherlands Twin-family study on Anxious Depression (NETSAD) (Boomsma *et al.*, 2000). Psychiatric diagnoses of the participants were obtained in 1997 by telephone interviews using the Composite International Diagnostic Interview (CIDI)(World Health Organization, 1992). For a detailed description of the data collection, see Boomsma *et al.* (2000) and Middeldorp *et al.* (2006). Data were used from participants with actual diagnoses within the last 12 months. The index diagnoses of the psychiatric

Table 1. Number of families per zygosity in the study with the number of twins and siblings per family

Number of siblings	0	1		2		
Sex of siblings		male	female	male/ male	female/ female	male/ female
MZM families						
2 twins	305	60	56	7	10	24
1 twin	26	4	8	0	1	2
MZF families						
2 twins	487	83	105	19	18	29
1 twin	37	3	5	0	2	3
DZM families						
2 twins	246	50	51	4	10	16
1 twin	27	3	3	0	1	2
DZF families						
2 twins	324	64	62	6	18	11
1 twin	38	1	9	1	3	3
DOS families						
2 twins	488	99	108	11	21	32
1 twin	46	2	10	1	2	2

MZM, monozygotic males; MZF, monozygotic females; DZM, dizygotic males; DZF, dizygotic females; DOS, dizygotic opposite sex

control group participants varied from depression, panic disorder and social phobia to general anxiety disorder. The population control group was obtained from the NETSAD study and was selected for absence of any diagnosis. The 68 participants were selected to match OCD participants in terms of age and sex.

Measures

The Young Adult Self Report (YASR) is a standardized self-report questionnaire for adolescents and adults (Achenbach, 1997). It is derived from the Child Behavior Checklist, a parent-derived rating instrument for children between 4-18-years old (Achenbach, 1997; Achenbach, 1991). The YASR roughly has the same format as the CBCL, except that items pertaining to childhood problems were replaced by items pertaining to adults' functioning. The YASR comprises 110 problem items, covering emotional and behavioral problems during the previous 6 months. The participants respond on a 3 point scale with the code of 0 for not true, 1 for somewhat or sometimes true and 2 for very true of often true. A good reliability and validity of the YASR has been reported by Achenbach (Achenbach *et al.*, 1987) and was supported for the Dutch version (Wiznitzer *et al.*, 1992; Ferdinand & Verhulst, 1995). The YASR-OCS contains the same 8 items as the CBCL-OCS (Nelson *et al.*, 2001), except that items are worded in the first person (Table 2). Using a cut-off of 5 on the CBCL-OCS, 91% of all DSM-determined OCD cases were identified in a clinical sample of children with reasonable specificity (67.2%) (Hudziak *et al.*, 2006). The CBCL-OCS showed also good reliability and validity in several other samples (Geller *et al.*, 2006; Storch *et al.*, 2006). A numerical value for the YASR-OCS is obtained by adding the scores on the relevant 8 items (0, 1 or 2 per item), thus limiting the scale to a range between 0 and 16.

DATA ANALYSES

Psychometric analyses

Internal consistency of the YASR-OCS was obtained by Chronbach's α coefficient. ROC analyses were conducted to determine the extent to which the YASR-OCS can accurately identify persons with OCD. ROC analysis uses the association between sensitivity [true positives/(true positives + false negatives)], and specificity [true negatives/(true negatives + false positives)] to derive an Area Under the Curve (AUC), which indicates how well a measure distinguishes between case positive (i.e., OCD group) and case negative (i.e., psychiatric controls or population controls) irrespective of the base rate. A value of .50 of the AUC indicates chance level and 1.0 indicates a perfect diagnostic tool. For detailed descriptions of the underlying principles of ROC analysis see Swets (1996) and McFall *et al.* (1999). We furthermore calculated Positive and Negative Predictive Values, respectively abbreviated as PPV [true positives/(true positives + false positives)], and NPV [true negatives/(true negatives + false negatives)]. ROC analyses were conducted with SPSS version 12 (SPSS for windows, 2003).

Genetic analyses

Genetic analyses include data from siblings in addition to MZ and DZ twins. This extension of the classical twin design provides increased statistical power,

Table 2. YASR items used for the YASR-OCS

YASR item no	YASR item	YASR syndrome on which item is scored
9	I cannot get my mind off certain thoughts	Thought problems
31	I am afraid I might think or do something bad	Anxious/depressed
32	I feel I have to be perfect	Anxious/depressed
52	I feel too guilty	Anxious/depressed
66	I repeat certain acts over and over	Thought problems
84	I do things other people think are strange	Thought problems
85	I have thoughts that other people would think are strange	Thought problems
112	I worry a lot	Anxious/depressed

YASR-OCS, Young Adult Self Report Obsessive-Compulsive Scale

both for gene detection (Dolan *et al.*, 1999) and for estimation of the genetic and common environmental influences (Posthuma & Boomsma, 2000; Stoel *et al.*, 2006). Genetic analyses decompose the variance of the liability to obsessive-compulsive (OC) symptoms into its genetic and environmental contributions. We assumed that twin resemblance arises from two latent factors, additive genetic factors (A) and shared environmental factors (C). MZ twins share all of their genes, whereas DZ twins and non-twin siblings share on average 50% of their segregating genes. Any familial resemblance due to genetic additive factors will therefore be higher for MZ twins than for DZ twins and non-twin siblings. Shared environmental factors, experiences shared by members of a twin pair that tend to make them similar, contribute equally to the correlation in MZ and DZ twins. In addition to A and C, the model also includes nonshared or individual-specific environment (E), which reflects measurement error and individual experiences that make members of a twin pair different in their liability to OC symptoms.

Because the data exhibited a pronounced right skew, we used a threshold model under the assumption of an underlying continuous liability distribution with the thresholds defining categories (Derks *et al.*, 2004). The thresholds are chosen in such a way that the prevalences are more or less similar in each of the categories. We used three thresholds, because the use of more thresholds had the disadvantage of the presence of empty cells. To correct for multiple testing, we tested each model in the sequence at a significance level (α) of .01. Genetic analyses were carried out in several steps using the software package Mx (Neale *et al.*, 2003).
We first fitted a saturated model in which thresholds and polychoric correlations between twin pairs, twin-sibling pairs, and sibling-sibling pairs were estimated without any restrictions. In model fitting procedures, the saturated model is used as a starting-point for the comparison of different, nested models. The fit and parsimony of the various nested models are judged using likelihood ratio tests in which the negative log-likelihood (-2LL) of the nested model is compared with -2LL of the saturated model. Subtracting the two -2LLs from each other yields a statistic that is asymptotically distributed as χ^2 with degrees of freedom (df) equal to the difference between the number of parameters in the two models. According to the principle of parsimony, models with fewer parameters are preferred if they do not give a significant deterioration of the fit. In addition, the Akaike Information Criterion (AIC) , a goodness-of-fit index that considers the rule of parsimony, was calculated.

The comparison of MZ twin pair correlations with DZ twin pair and sibling pair correlations provides a first estimate of the sources of variation in individual differences in OC symptoms. Furthermore, to test whether a specific twin-factor influences individual differences in OCS, we tested for heterogeneity of correlations between DZ twins and siblings. If DZ correlations are not equal to sib-sib correlations or twin-sib correlations, it indicates the existence of a special twin environment.

Next, a threshold model was used to partition the variance of the underlying liability for OC symptoms into additive genetic (A), shared environmental (C) and nonshared or individual-specific environment (E). Analyzing all zygosity groups (i.e. male MZ twin pairs and DZ twin/sib pairs, female MZ twin pairs and DZ twin/sib pairs, DZ opposite sex twin/sib pairs) enabled us to examine two different sex effects. The magnitude of the genetic and environmental influences was constrained to be equal for men and women to test if the importance of the genetic and environmental factors is similar for men and women. By constraining the genetic correlation for opposite sex pairs to .5, an explicit test was conducted whether the same genetic factors operate in males and females.

RESULTS

Psychometric analyses

ROC analyses showed an AUC of .84 (95% CI = .78-.91) on the YASR-OCS when compared to clinical controls. When compared to general population controls, the AUC was .95 (95% CI = .92-.99). At the best cut-off point of 7, the sensitivity was 82.4% and the specificity was 69.7% when compared to clinical controls.

The PPV and NPV were 73.7% and 79.3% respectively. The Cronbach's α coefficient for the 8 items of the YASR-OCS was .69.

Genetic analyses

All thresholds for OC symptoms could be constrained to be equal for both twins in pairs ($\chi^2(12) = 7.34$, $p = .83$), in same-sex and opposite sex dizygotic pairs ($\chi^2(18) = 20.0$, $p = .33$), in monozygotic and dizygotic same-sex pairs ($\chi^2(30) = 38.3$, $p = .14$), and sibs and twins ($\chi^2(36) = 43.8$, $p = .17$). Thresholds for men and women were different ($\chi^2(33) = 261.7$, $p = < .001$) with lower thresholds for women than men, indicating a higher prevalence in women in OC behavior.

Table 3 displays the correlations of the 5 different zygosity groups. The siblings are included in the DZ groups, because, comparing with the fully saturated model, all sibling correlations could be constrained to be equal to the DZ correlations for males and females ($\chi^2(70) = 89.3$, $p = .16$), showing that there was no specific twin environment. The MZ correlations are substantially higher than the DZ correlations for both men and women, suggesting that shared environmental effects do not contribute to individual differences in OC behavior. For both males and females, MZ twin correlations are clearly different from unity, indicating nonshared environmental effects on the YASR-OCS.

Table 3. Twin correlations on YASR-OCS scores by zygosity

MZM	MZF	DZM/sibsMM	DZF/sibsFF	DOS/sibsOS
0.44	0.50	0.13	0.26	0.21

YASR-OCS, Young Adult Self Report Obsessive-Compulsive Scale MZM, monozygotic males; MZF, monozygotic females; DZM, dizygotic males; DZF, dizygotic females; DOS, dizygotic opposite sex; sibsMM, brothers; sibsFF, sisters; sibsOS, sibs of opposite sex

The results of genetic model fitting are summarized in Table 4. The ACE model (model 2) describes the data adequately when compared with the fully saturated model (model 1). Next, a model was fitted without the shared environmental effect (model 3). The fit did not get significantly worse. In model 4 we constrained the correlation of the genetic factors for opposite sex twins to be 0.5. This did not give a significant deterioration in fit, which suggests that the same genes account for variation in OC behavior in men and women. In model 5 we constrained the magnitude of the effect of the genetic risk factors to be the same in men and women. This model just fits the data, suggesting no differences in heritability between men and women. However, according to the AIC, model 4 has a lower AIC value in comparison to model 5. So according to the AIC, model 4 would be the model of choice. The AIC adjust χ^2 for the number of estimated parameters and can sometimes give another result than a likelihood ratio test.

Model 4 estimated the heritability of OC behavior to be 39% for men and 50% for women. Model 5 estimated the heritability of OC behavior to be 47% for both men and women. The remaining variance in liability for OC symptoms was attributed to nonshared environment.

DISCUSSION

This is the first adult twin-family study which investigated sex-effects in the influence of genetic and environmental factors on individual differences in OC behavior in a large population-based sample of twins and sibs. Five major conclusions can be drawn. Firstly, the YASR-OCS appears to be an effective instrument to screen for OCD in adults. Secondly, MZ and DZ twins did not differ from their siblings for prevalence of OC symptoms and DZ twins did not differ from siblings for resemblance of OC symptoms, so the results of our study generalize to non-twins. Thirdly, we found a modest heritability of individual differences in OC behavior. Individual specific environment accounted for the remaining variance of OC behavior. Fourthly, depending on the fit-index the results suggest that there are small or no sex differences in the importance of genetic and environmental influences between men and women. Fifth, because the genetic correlation for opposite sex pairs could be constrained to .5, the genes which account for the genetic influence seem to be the same in both sexes.

Psychometric analyses

The YASR-OCS showed satisfactory psychometric properties with a sensitivity and specificity of 82% and 70%. These findings are comparable with the performance of the CBCL-OCS, which demonstrated a sensitivity and specificity of 92% and 67% in children. A major advantage of these two instruments is the fact that they provide investigators and clinicians with two fully comparable screeners on OC symptomatology along the lifespan. Course and stability over time of OC behavior with a follow-up period covering childhood, adolescence as well as adulthood, using age-adjusted instruments have advantages over instruments developed for one age period only (Wiznitzer *et al.*, 1992). The YASR-OCS is an instrument that seems to effectively deal with the discontinuity in available diagnostic and research tools between children and adolescents on the one hand and adults on the other.

Genetic analyses

Our results on genetic contribution are in line with those found by Clifford *et al.* (1984), but our heritability

Table 4. Model fitting results for heritability of YASR-OCS scores

Number of model	Type of model[a]	-2LL	χ^2	df	p[b]	AIC	Compared with model
1	Fully saturated model	18477.0	-	-	-	-	-
2	ACE, quantitative and qualitative sex differences allowed	18630.7	153.7	121	.02	4252.7	1
3	AE, quantitative and qualitative sex differences allowed	18630.9	.2	2	.90	4248.9	2
4	AE, quantitative sex-differences allowed, but no qualitative sex differences	18631.0	.1	1	.75	4247.0	3
5	AE, no quantitative and qualitative sex differences allowed	18636.0	5.0	1	.03	4250.0	4

[a] A=additive genetic effects; C=common or shared environmental effects; E= nonshared or individual-specific effects. Quantitative sex differences=sex differences in magnitude of heritability. Qualitative sex differences=sex differences in genetic risk factors.
[b] Significance level (α) was set at .01.

estimates are somewhat higher than estimates in women by Jonnal *et al.* (2000). Like Jonnal *et al.* (2000) and Clifford *et al.* (1984), we did not observe shared environmental influences on OC behavior in adults. In children, a modest influence of shared environment has been found especially at age 12 (Hudziak *et al.*, 2004; van Grootheest *et al.*, 2007). This finding might indicate a special period around adolescence for OC behavior, during which individuals are sensitive to the effects of the home environment. This is in line with a study of Geller *et al.* (2001) on developmental aspects of OCD in three groups, children, adolescents and adults. Specific clinical correlates and symptom profiles were associated with the disorder in different age groups and these findings supported a hypothesis of developmental discontinuity between juvenile and adult OCD.

In general, OC behavior showed a moderate heritability in line with other internalizing phenotypes, like general anxiety disorder (Hettema *et al.*, 2001), panic disorder (Kendler *et al.*, 2001) or depression (Kendler & Prescott, 1999). The heritabilities we found for adults are close but less high than the heritabilities of approximately 55% in the children sample of Hudziak *et al.* (2004). Obviously, the adult sample in this study included early-onset cases with OC symptomatology, in several studies associated with increased family history, as well as late-onset cases, associated with lower genetic load. The latter may temper the heritability in adults.

Our results suggest that there are small or no sex differences in heritability of OC behavior, depending on the choice of fit-index. This means that further research is needed before one can conclude definitely on the existence of quantitative sex-differences. In children, Hudziak *et al.* (2004) found no evidence for quantitative differences. In several familystudies no gender differences were found in patients with a positive family history (Nestadt *et al.*, 2000b; Chabane *et al.*, 2005; Delorme *et al.*, 2005). On other hand, we found small sex differences in thresholds, with lower thresholds for women. This means that the prevalence for women is somewhat higher than for men, which seems to support earlier findings of a slight preponderance in prevalence of OC symptoms in women (Nestadt *et al.*, 1998; Crino *et al.*, 2005; Torres *et al.*, 2006).

The conclusion that largely the same genes may account for OC behavior in men and women has implications for molecular genetic research. Our results emphasize the feasibility of treating OC behavior as a quantitative trait to which a QTL approach can be applied, besides the approach of categorical analyses of clinical OCD cases (Miguel *et al.*, 2005). Further, these findings suggest that data of men and women can be pooled in molecular genetic analyses. This conclusion may seem in contrast with, for example, two recent association studies, which found the glutamate transporter gene SLC1A1 to be associated with susceptibility to OCD, particularly in males (Dickel *et al.*, 2006; Arnold *et al.*, 2006). However, one should realize that our results reflect the sum of all possible genetic effects associated with OC behavior, which by does not rule out a small sex effect of a single candidate gene.

Limitations

The results of this study should be interpreted in the context of four potential methodological limitations. Firstly, the modest number of items in the YASR-OCS may contribute to increased error variance. Secondly, the YASR-OCS is only specific to recent symptoms, not lifetime symptoms, as it measures symptoms of the last 6 months. Thirdly, the genetic and environmental contributions presented in this report reflect YASR-OCS scores, not clinical measures of DSM-IV OCD. Although the YASR-OCS showed satisfactory criterion validity for DSM-IV OCD cases, we used the whole distribution of OC symptoms in the population with the underlying assumption that OCD reflects the end of a normal distribution,

while OC symptoms represent a milder form of the latter (Jonnal *et al.*, 2000; van den Oord *et al.*, 2003; Kendler, 2005). A quantitative approach does justice to the fact that previous studies found high rates of subclinical OC symptoms in family members of OCD probands (Pauls *et al.*, 1995; Nestadt *et al.*, 2000b), which in a DSM-dichotomous approach would be missed (Miguel *et al.*, 2005). Since the YASR-OCS is developed as a short screening instrument, it was not possible to distinguish various symptom dimensions within OCD (Mataix-Cols *et al.*, 2005). Fourth, the findings of this analysis are predicated on the assumptions of the method used. These assumptions include absence of assortative mating and the equal environment assumption (EEA). Maes *et al.* (Maes *et al.*, 1998) found that significant but moderate primary assortment exists for psychiatric disorders but concluded that the bias in twin studies caused by the small amount of assortment is negligible. Jonnal *et al* (2000) tested the EEA for OC symptoms and concluded that the EEA was not violated.

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CHAPTER 5

Marital resemblance for obsessive-compulsive, anxious and depressive symptoms in a population-based sample

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Marital resemblance for obsessive-compulsive, anxious and depressive symptoms in a population-based sample

van Grootheest, D. S., van den Berg, S. M., Cath, D. C., Willemsen G. & Boomsma, D. I.

ABSTRACT

Background Resemblance between spouses can be due to phenotypic assortment, social homogamy and/or marital interaction. A significant degree of assortment can have consequences for the genetic architecture of a population. We examined the existence and cause(s) of assortment for Obsessive-Compulsive (OC), anxious and depressive symptoms in a population based twin-family sample.

Methods OC, anxious and depressive symptoms were measured in around 1400 twin-spouse and over 850 parent pairs. Correlations of twins and their spouse, twin and co-twin's spouse, spouses of both twins and parents of twins were obtained to consider phenotypic assortment versus social homogamy as possible causes of marital resemblance. The association of length of relationship with marital resemblance was also investigated. Finally we examined if within-trait or cross-trait processes play a primarily role in marital resemblance.

Results Small but significant within-trait correlations between .1 and .2 were seen for spouse similarity in OC, anxious and depressive symptoms. Cross-correlations were significant but lower. There was no correlation between length of relationship and marital resemblance. From the pattern of correlations for twin-spouse, co-twin-spouse and spouses of both twins phenotypic assortment could not be distinguished from social homogamy. Both within- and cross-assortment processes play a role in marital resemblance.

Conclusions Small within- and across-trait correlations exist for OC, anxious and depressive symptoms. No evidence for marital interaction was found. Spouse correlations are small, which makes it difficult to distinguish between social homogamy and phenotypic assortment. It is unlikely that correlations of this size will have a large impact on genetic studies.

In many psychiatric disorders, several substance disorders and in antisocial personality disorder, marital resemblance has been found, meaning that married partners are more similar on some phenotypic traits than would be expected by chance (Merikangas, 1982). Findings for depressive and anxiety disorders though are not unequivocal. For anxiety disorder, some studies found no evidence of increased risk of anxiety disorder in spouses of patients with an anxiety disorder (Eagles *et al.*, 1987; Low *et al.*, 2007), but several other studies found an increased risk (Tambs, 1991; Zimmermann-Tansella & Lattanzi, 1991; McLeod, 1995; Galbaud du *et al.*, 1998; Dubuis-Stadelmann *et al.*, 2001) with spousal correlations varying between .1 and .3. Only one study mentioned data on marital resemblance for Obsessive-Compulsive Disease (OCD). Mathews *et al.* (2007) conducted a linkage study with OCD and found 19 mating pairs with known OCD status for both spouses. In two of these pairs (10%), both members had OCD or clinically significant Obsessive Compulsive (OC) symptoms which may be an indication that assortative mating exists for OCD.

For depressive disorders, a review and a meta-analysis were conducted by Mathews and Reus (2001). Twelve of 17 studies reported marital resemblance for depression. Results of the meta-analysis supported these findings, and indicated that marital resemblance occurs in major depression, with odds ratios for the combined data of 2.38. One of the most extensive studies on spousal correlation for psychiatric disorders in a population-based sample was carried out by Maes *et al.* (1998). Several psychiatric diagnoses were examined, including generalized anxiety disorder, major depressive disorder, panic disorder and phobias. A small degree of assortment with correlations between .1 and .2 was seen within and across psychiatric diagnoses.

Marital resemblance is likely due to a multifactorial process, including phenotypic assortment, social homogamy, and marital interaction (Reynolds *et al.*, 2006). Phenotypic assortment means that partner selection is based directly on the partner's phenotype; there is a preference for a phenotype like one's own, resulting in marital resemblance. A variant of the latter, called secondary phenotypic assortment, encompasses partner selection that occurs on the basis of variables that correlate with the phenotype under study, such as demographic variables or personality characteristics. As in several other studies (Galbaud du *et al.*, 1998; Dubuis-Stadelmann *et al.*, 2001), Maes *et al.* found (1998) that only a small amount of the observed marital resemblance for mental illness could be explained by assortment of correlated variables, such as age, religious attendance and education.

Social homogamy refers to the tendency for individuals to have partners with similar social background. Whereas phenotypic assortment refers to the selection of a partner based on the observed phenotype, which may or may not be influenced by genetic factors, social homogamy refers to assortment based on the social background (Heath & Eaves, 1985; Reynolds *et al.*, 2006). Under social homogamy partner selection takes place within social strata, which are correlated with the phenotype under study. An example of social homogamy was found recently by Reynolds *et al.* (2006) for tobacco use, implying that one may be socially associated with those among whom tobacco use is common or uncommon due to for example social contacts through one's family or network of friends.

Marital interaction or shared influences after marriage refers to a process of mutual influences between spouses living together (Penrose, 1944). In addition to the process of initial assortment, spouses may become more similar the longer they are married due to mutual influence between spouses or by sharing the same pathologic factors. Contagion is a special case of marital interaction where illness of one partner is a direct consequence of the breakdown of the other (Maes *et al.*, 1998).

For twin and family studies examining psychiatric disorders or traits, it is important to know if marital resemblance exists. Non-random mating due to phenotypic assortment will lead to an increase in genetic variance in the offspring generation and to an increase in resemblance among siblings and between parents and offspring (Fisher, 1918; Wright, 1921; Crow & Felsenstein, 1968), whereas social homogamy and marital interaction do not lead to increased genetic resemblance (Falconer & Mackay, 1996).

In the present study we aim to examine the existence of marital resemblance for OC, anxious and depressive symptoms within a population-based sample of twins, their partners and their parents. Because we included the partners of the twins (Heath & Eaves, 1985; Reynolds *et al.*, 2000), the present study is the first one that may, given sufficiently high correlations, disentangle the causes of spouse similarity in OC, anxious, and depressive symptoms. Furthermore, because data from two generations are included (from twins and partners plus parents of twins), data from couples with different lengths of time spent together are available. This allows for the examination of the correlation between length of marriage and similarity in psychiatric symptoms, i.e., marital interaction. We addressed the following questions:

1. Is there a significant association within and across OC, anxious and depressive symptoms between husbands and wives?
2. Can marital resemblance be explained by phenotypic assortment, social homogamy or both?
3. Is marital resemblance influenced by marital interaction?
4. Does mate selection occur primarily within or across OC, anxious and/or depressive symptoms?

METHODS

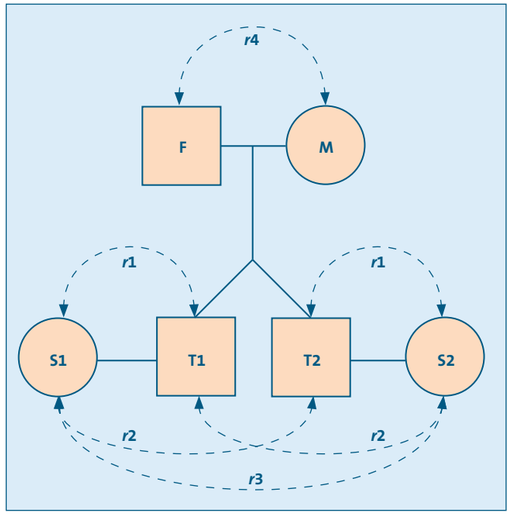
Participants

This study is part of an ongoing longitudinal survey study of the Netherlands Twin Register (NTR), which has assessed families with adolescent and adult twins roughly every two years since 1991. Each survey, with the exception of the 1995 wave, collected information on personality and psychopathology. Sample selection and response rates are described in detail in Boomsma *et al.* (2002; 2006). For this study, data from twins, their partners and parents of twins from the 2002 survey were used. We received complete surveys for OC, anxious and depressive symptoms of respectively 4406, 4382 and 4414 twins, 1442, 1439 and 1464 partners of twins, and 2189, 2167 and 2200 parents of twins. Table 1 shows the numbers of complete spouse pairs, i.e., pairs of which both members filled in a complete survey for the different phenotypes. The mean ages of the subjects at the time of the survey were 32.8 years (SD 11.3) for twins, 36.0 years (SD 12.0) for their partners and 56.3 years (SD 5.9) for the parents of the twins.

Table 1. Number of complete pairs per relationship for questionnaires on OC, anxious and depressive symptoms

	Complete pairs (n)		
	OC symptoms	Anxious symptoms	Depressive symptoms
Twin-spouse	1416	1441	1407
Cotwin-spouse	1090	1110	1083
Spouse1 - spouse2	264	272	263
Parents	875	881	857

Figure 1. Schematic representation of a family including the correlations



T, twin; S, spouse; F, father; M, mother; r1= twin-spouse correlation; r2= cotwin-spouse correlation; r3=spouse-spouse correlation; r4= parents correlation

Table 2. Definitions with expectations of the patterns of correlations

Marital resemblance:
mated pairs are more similar for a phenotypic trait, than would be expected by chance: r1>0 and r4>0

Phenotypic assortment:
partner selection is based on phenotype: r1>r2>r3 and correlations MZ>DZ for r2 and r3

Social homogamy:
non-random assortment due to shared environment: r1=r2=r3 and correlations MZ=DZ for r2 and r3.

Marital interaction:
process of interaction between partners living together leading to resemblance: r4>r1 and a significant correlation between length of relationship and resemblance.

r1= twin-spouse correlation; r2= cotwin-spouse correlation; r3=spouse-spouse correlation; r4= parents correlation

Measures

OC symptoms were measured by 12 items of the Padua Inventory (Sanavio, 1988), translated into Dutch, revised and validated by Van Oppen *et al.* (1995). Items were chosen from each OC subscale of the Padua Inventory Revised. The sensitivity and specificity for the 12 items to detect OCD was .74 and .72 respectively, when comparing a group of OCD patients with clinical controls (Cath *et al.*, 2008). The positive and negative predictive values (PPV and NPV) were 53.1% and 86.7% respectively. Cronbachs' α of the scale in the current study sample was 0.79. Depression was assessed with the subscale anxious-depressed of the Young Adult Self Report (YASR) (Achenbach, 1997). Good reliability and validity for the anxious-depressed subscale of the American YASR have been reported by Achenbach (1997) with a Cronbachs' α of .91 and a test-retest validity of .89 and were supported for the Dutch version (Wiznitzer *et al.*, 1992, Ferdinand *et al.*, 1995). Reliability of the scale in the current study sample was 0.86. Anxiety was measured with the Dutch translation of the Spielberger State Trait Anxiety Inventory – trait version (STAI) (Spielberger, 1983; Ploeg van der, 2000) and showed test-retest reliabilities ranging from .73 - .92. The Cronbachs' a coefficients of the STAI in the current sample is .92. The STAI measures general anxiety and is strongly associated with several DSM-IV anxiety disorders, particularly Generalized Anxiety Disorder (Middeldorp *et al.*, 2006).

Analyses

Familial correlations were obtained by maximum-likelihood estimation in Mx (Neale *et al.*, 2003). Figure 1 displays the different familial correlations: twin-spouse correlations ($r_{twin\text{-}spouse}$), cotwin-spouse correlations ($r_{cotwin\text{-}spouse}$), spouse1-spouse2 correlations ($r_{spouse1\text{-}spouse2}$) and parent-parent correlations ($r_{parents}$). The pattern of correlations provides the key information for resolving assortment mechanisms (table 2). If phenotypic assortment is the exclusive assortment process, the expected pattern of correlations will conform to the following pattern $r_{twin\text{-}spouse} > r_{cotwin\text{-}spouse} > r_{spouse1\text{-}spouse2}$ (Reynolds et al, 2006). Furthermore, the magnitude of the $r_{cotwin\text{-}spouse}$ and $r_{spouse1\text{-}spouse2}$ will be higher in Monozygotic (MZ) kinships than in Dizygotic (DZ) kinships if heritable influences are present. If social homogamy is the exclusive assortment process, then the $r_{twin\text{-}spouse}$, $r_{cotwin\text{-}spouse}$ and $r_{spouse1\text{-}spouse2}$ will all be similar to one another and across zygosity assuming perfect selection for social background environmental variance and equal magnitudes of social background influences in women and men. If there is imperfect selection, and the magnitude of social background influences for men and women differs, spousal correlation will then be rather similar to correlations under phenotypic assortment. We then expect $r_{twin\text{-}spouse} = r_{cotwin\text{-}spouse} > r_{spouse1\text{-}spouse2}$ (Reynolds et al, 2006). Under social homogamy no MZ-DZ differences in the magnitude of $r_{cotwin\text{-}spouse}$ and $r_{spouse1\text{-}spouse\,2}$ are expected. Thus, when both genetic and shared environmental factors play a role, phenotypic assortment can only be distinguished from social homogamy by the differences in MZ and DZ families for $r_{cotwin\text{-}spouse}$ and $r_{spouse1\text{-}spouse2}$ and that $r_{twin\text{-}spouse} > r_{cotwin\text{-}spouse.}$

If marital resemblance is due to marital interaction, we expect the $r_{parents}$ to be larger than $r_{twin\text{-}spouse}$, as spouses in the parental generation are in general married longer than spouses in the offspring generation. We calculated correlations between length of relationship and marital resemblance, for twin-spouse pairs and parents in one analysis and within the two generations (i.e., separate analyses for twin-spouse pairs and parents). For this purpose, marital resemblance was defined by the absolute difference in scores on the phenotypes for two partners; closer to zero indicating a larger resemblance. Length of relationship was defined by the length of the present relationship in years.

To study if marital resemblance occurs primarily within or across OC, anxious and/or depressive symptoms, we examined assortment between OC, anxious and depressive symptoms at once, using the conditional path method (Carey, 1996). For this method, the observed matrix of spousal correlations is decomposed into 1) the matrix of correlations within husbands (Rh); 2) the matrix of correlations within wives (Rw) and; 3) the matrix of correlations between the disorders of husbands and the disorders of wives (D) (Phillips *et al.*, 1987, Maes *et al.*, 1998). The latter matrix is modelled by a conditional path matrix of latent direct assortment effects. As an example, we specify this model in matrix notation as follows (for two traits):

$$M = \begin{pmatrix} 1 & h \\ h & 1 \end{pmatrix} \times \begin{pmatrix} d11 & d12 \\ d21 & d22 \end{pmatrix} \times \begin{pmatrix} 1 & w \\ w & 1 \end{pmatrix} = \begin{pmatrix} d11 + hd21 + d12w + hd22w & d11w + hd21w + d12 + hd22 \\ hd11 + d21 + hd12w + d22w & whd11 + d21w + hd12 + d22 \end{pmatrix}$$

The first matrix contains the correlation between traits in husbands, the third matrix the correlation between traits in their wives. The matrix D can be thought of as the direct assortment effects of the correlations between husbands and wives after the correlations due to assortment for other, correlated variables has been partialled out (Maes *et al*, 1998). The diagonal of the resulting matrix M has the within trait correlations on the diagonal. As can be seen, these are a function of the direct assortment for the first trait (d11), plus assortment for the second trait and assortment across traits, if there is association between traits in husbands and/or wives. We estimated the D matrix and tested if within and/or across variables were significantly different from zero by comparing the increase in χ^2 to the increase in degrees of freedom for the different models. For all analyses the statistical package Mx was used to estimate and test the equality of the correlations (Neal *et al.*, 2003).

RESULTS

Table 3 shows twin-spouse, cotwin-spouse, spouse1-spouse2 and parental correlations for OC, anxious, and depressive symptoms for all zygosity groups. We also present cotwin-spouse and spouse1-spouse2 correlations constrained to be equal for MZ twin and DZ twins, and all correlations constrained to be equal across all zygosity groups. Between brackets, the number of complete twin pairs per relationship is shown.

For OC symptoms, cotwin-spouse and spouse1-spouse2 correlations of MZ families and DZ families show some variety of values across different types of twin pairs, especially when the number of twin pairs is lower (e.g. spouse1-spouse2). Correlations could not be distinguished from each other, making it impossible to to discriminate between phenotypic assortment and social homogamy. For all four types of pairings correlations could be constrained to be equal across the five zygosity groups. Spouse similarity is small (r = .16), but significantly ($\chi^2(1) = 32.0$, $p < .001$) higher than zero. Similarity drops among other pairings, i.e., $r_{twin\text{-}spouse} > r_{cotwin\text{-}spouse} > r_{spouse1\text{-}spouse2}$. Such a pattern among the in-laws suggests phenotypic assortment, but confidence intervals overlap around correlations. So correlations do not significantly differ from each other and social homogamy cannot be ruled out. The spouse similarity in parents is .15. This is not significantly different ($\chi^2(1) = .212$, $p = .65$) from the correlation in the younger generation, which suggests absence of marital interaction. This is confirmed by the fact that no significant correlation was found across generations (r = -.02) and within generations (twin-spouse: r = -.04, parents: r = .05) between duration of relationship and marital resemblance of OC symptoms.

For anxious symptoms, we see a similar pattern as for OC symptoms. The twin-spouse correlation is .16. No MZ and DZ differences are seen for cotwin-spouse and spouse1-spouse2 correlations. Although a pattern of $r_{twin\text{-}spouse} > r_{cotwin\text{-}spouse} > r_{spouse1\text{-}spouse2}$ is seen, confidence intervals overlap for the correlations for the different pairings. $r_{parents}$ practically equals $r_{twin\text{-}spouse}$ and no significant correlation between length of relationship and marital resemblance of anxiety was seen across generations (r = -.01) and within generations (twin-spouse: r = -.03, parents: r = -.02).

For depressive symptoms, a twin-spouse correlation of .19 was found. MZ families show correlations similar to those of DZ families for cotwin-spouse and spouse1-spouse2 correlations. A pattern of $r_{twin\text{-}spouse} > r_{cotwin\text{-}spouse} > r_{spouse1\text{-}spouse2}$ is seen, but again there is overlap in the confidence intervals. $r_{parents}$ is significantly lower ($\chi^2(1) = 8.79$, $p < .01$) than $r_{twin\text{-}spouse}$, which would even suggest that the longer the relationship, the lower the similarity between partners for depression. However, no significant correlation between duration of the

Table 3. Familial correlations per relationship by zygosity for OC, anxious and depressive symptoms. Number of complete twin pairs per relationship are presented between brackets

	Equal across monozygotic twins (CI)	Equal across dizygotic twins (CI)	Equal across all zygosities (CI)			
				mzm	dzm	mzf	dzf	dos
a) OC symptoms								
r1 Twin-spouse	.19 (.14 - .24)	.11 (.08 - .15)	.15 (.10 - .20)	.19 (216)	.11 (103)	.17 (536)	.05 (263)	.17 (231)
r2 Cotwin-spouse	.08 (.00 - .16)	.07 (-.02 - .17)	.08 (.01 - .14)	.06 (161)	.32 (72)	.09 (464)	-.04 (201)	.17 (259)
r3 Spouse1-spouse2	-.06 (-.22 - .11)	.12 (-.02 - .27)	.04 (-.07 - .15)	-.07 (41)	.28 (15)	-.06 (121)	.20 (41)	-.03 (46)
r4 Parents			.15 (.08 - .21)	.20 (152)	.21 (91)	.19 (264)	.13 (155)	.07 (213)
b) Anxious symptoms								
r1 Twin-spouse	.19 (.14 - .24)	.16 (.11 - .22)	.16 (.11 - .22)	.19 (223)	.16 (107)	.17 (538)	.23 (265)	.09 (308)
r2 Cotwin-spouse	.10 (.04 - .17)	.11 (.01 - .20)	.11 (.05 - .17)	.06 (169)	.09 (72)	.14 (464)	.02 (206)	.19 (199)
r3 Spouse1-spouse2	-.02 (-.15 - .11)	.06 (-.10 - .22)	.01 (-.13 - .14)	-.01 (43)	.58 (14)	.02 (122)	-.01 (44)	-.14 (49)
r4 Parents			.18 (.12 - .24)	.16 (154)	.22 (91)	.22 (265)	.23 (156)	.10 (215)
c) Depressive symptoms								
	MZM	**DZM**	**MZF**	**DZF**	**DOS**			
r1 Twin-spouse	.16 (221)	.10 (107)	.26 (527)	.23 (254)	.11 (298)			
r2 Cotwin-spouse	.10 (167)	.21 (71)	.10 (453)	.10 (199)	.09 (193)			
r3 Spouse1-spouse2	-.18 (42)	-.42 (14)	-.09 (118)	.09 (41)	-.09 (48)			
r4 Parents	.17 (149)	.17 (89)	.11 (252)	.03 (156)	.01 (211)			

r, correlation; MZM, monozygotic male; DZM, dizygotic male; MZF, monozygotic female; DZF, dizygotic female; DOS, dizygotic opposite-sex twin pairs; CI, Confidence Intervals

relationship and marital resemblance of depression was found across generations (r = .01) or within generations (twin-spouse: r = -.04, parents: r = .03).

Significant spousal correlations across OC, anxious and depressive symptoms were found for both twin-spouses and parents in the range of .07 - .11 (table 4a). The across symptoms assortment correlations were lower than the within symptoms assortment correlations. Like the within symptoms assortment correlations a pattern of $r_{twin\text{-}spouse} > r_{cotwin\text{-}spouse} > r_{spouse1\text{-}spouse2}$ is also seen for the across symptoms correlations with overlapping confidence intervals (data not shown). No differences in correlations were seen for twin-spouses or parents. These results indicate that both within and cross assortment processes play a role.

To further explore this hypothesis, all traits were studied at once using the conditional path method. Because the correlations of the twin-spouse sample were not different from those of the parents ($\chi^2(6) = 6.47$, p = .37), results of the joint analysis of the two samples are presented. We tested whether sex-differences existed in cross-assortment by testing for the symmetry of matrix D. This test yielded a nonsignificant result ($\chi^2(6) = 6.14$, p = .41) implying that sex is not a factor in the pattern of assortment for these traits. Subsequently, it was examined if the cross-assortment parameters could be constrained at zero without a significant loss of fit, but this was not the case ($\chi^2(3) = 19.3$, p < .01). We then fixed the within-trait assortment correlations to zero, allowing for cross-trait assortment, but this resulted in a even larger increase of the χ^2 ($\chi^2(3) = 39.2$, p < .01). This multivariate analysis suggests that both within- and cross-assortment for OC, anxious and depressive symptoms exists. Table 4b shows the estimates of the D-matrix. As the cross-correlations within a person (table 4c) are quite high, we expect the D-matrix estimates, which are controlled for cross-correlations within a person, to be different from the observed matrix (table 4a). This effect can especially be seen in the cross-assortment correlations (off-diagonal). Both cross-correlations with anxious symptoms are negative in the D-matrix, the opposite of the observed correlations in table 4a. The OC-Depressive symptoms correlation is comparable with the observed correlations. It appears that, after controlling for cross-correlations within a person, partners with anxious symptoms avoid partners with depressive or OC symptoms.

Table 4.

a) Observed cross-correlations for OC, anxious and depressive symptoms. Data of twin-spouses and parents have been pooled

	Spouse 1		
Spouse 2	**OC symptoms (CI)**	**Anxious symptoms (CI)**	**Depressive symptoms (CI)**
OC symptoms	.15 (.11 - .20)		
Anxious symptoms	.09 (.05 - .14)	.17 (.13 - .22)	
Depressive symptoms	.11 (.07 - .15)	.07 (.02 - .12)	.13 (.10 - .17)

b) Estimated cross-correlations of direct assortment for OC, anxious and depressive symptoms. Data of twin-spouses and parents have been pooled (D matrix)

	Spouse 1		
Spouse 2	**OC symptoms (CI)**	**Anxious symptoms (CI)**	**Depressive symptoms (CI)**
OC symptoms	.10 (.04 - .16)		
Anxious symptoms	-.07 (-.12 - -.01)	.25 (.15 - .33)	
Depressive symptoms	.10 (.04 - .15)	-.11 (-.19 - -.03)	.01 (-.08 - .10)

c) Within person cross-correlations for OC, anxious and depressive symptoms. Data of twin-spouses and parents have been pooled, correlations of husband and wives have been constrained to be equal (H or W matrix)

	OC symptoms (CI)	**Anxious symptoms (CI)**	**Depressive symptoms (CI)**
OC symptoms	1.00		
Anxious symptoms	.50 (.48 - .52)	1.00	
Depressive symptoms	.49 (.47 - .51)	.71 (.70 - .72)	1.00

CI, confidence intervals

DISCUSSION

This study examined the existence and possible cause of marital resemblance for OC, anxious, and depressive symptoms. Several importing findings emerged that are relevant for both future research and clinical practice. First, small but significant within- and cross-marital resemblance exists for OC, anxious, and depressive symptoms. Second, since correlations are small, it is difficult to distinguish between social homogamy and phenotypic assortment as the main cause of marital resemblance for OC, anxious and depressive symptoms. Third, no evidence was found for marital interaction. Fourth, both within- and cross assortment play a role in marital resemblance.

This is the first study that has examined marital resemblance for OC symptoms. The degree of correlations between partners for OC symptoms resembles those for depression and anxiety. Our findings for depression support the results of the meta-analysis of Mathews and Reus (2001), who found little, but significant marital resemblance for affective disorders. The finding of marital resemblance for anxiety symptoms in this study confirms various earlier rapports in both clinical and population-based studies (Tambs, 1991; Zimmermann-Tansella & Lattanzi, 1991; McLeod, 1995; Maes *et al.*, 1998; Galbaud du *et al.*, 1998; Dubuis-Stadelmann *et al.*, 2001), reporting correlations between .1 and .3 using either diagnostic or dimensional ratings of anxiety. Two studies did not find marital resemblance for anxiety disorders. Eagles *et al.* (1987) assessed anxiety in a population-based sample of elderly couples aged over 65. They actually found a small, but significant, correlation of .07. Recently, Low *et al* (2007) did not find spousal concordance for DSM-III anxiety disorders in a mixed patient/community sample (71.3% / 29.7%). The latter study is the only study on anxiety disorders which also included patients, while all other studies were based on community samples to overcome the problem of selection bias. This selection bias usually causes an overrepresentation of affected couples in clinical samples (Galbaud du *et al.*, 1998).

Besides clear significant assortment within traits, evidence for cross-assortment was found as well. The cross-assortment correlations were somewhat smaller than the within-assortment correlations This could suggest that within-assortment occurs primarily within the various anxious-depressive traits, but by comparing models it appeared that cross-assortment played a significant role as well, confirming results of Maes *et al.* (1998). Results from direct assortment estimations,

which have been controlled for comorbity, indicate that anxious partners tend to choose anxious partners, but avoid partners with OC behavior or depressive behavior. As we are the first study to report on these assortment estimations, replication of these latter results are needed.

The present study attempted to test whether social homogamy or phenotypic assortment is the underlying factor in resemblance of psychiatric diseases, since we had information on the spouses of identical and fraternal twins. We found roughly the same pattern of correlations for OC, anxious and depressive symptoms. Since the correlations are small with confidence intervals overlapping, we were unable to distinguish between social homogamy and phenotypic assortment processes. With such small correlations, extremely large numbers of twins and spouses are needed to be able to distinguish between different mechanisms. On the other hand, it is also possible that both mechanisms play a role; if this is the case the observed correlations are simply too small to have reasonable power to distinguish and estimate the magnitude of these different sources.

Nevertheless, there is reason to suspect that phenotypic assortment is a more probable mechanism, since shared environmental effects hardly seem to play a role in the occurence of OC symptoms and OCD (van Grootheest *et al.*, 2005), depression (Sullivan *et al.*, 2000) or anxiety disorders (Hettema *et al.*, 2001). The three existing adult studies on OCS did not find shared environmental factors to be important (Clifford *et al.*, 1984; Jonnal *et al.*, 2000, van Grootheest *et al.*, 2007). For depression, no evidence for shared environmental factors was found in a meta-analysis of Sullivan *et al.* (2000). For anxiety disorders, only generalized anxiety disorder showed an uncertain but small role for shared environmental factors. For other anxiety disorders, no role for shared environmental factors was found (Hettema *et al.*, 2001).

We did not find evidence for marital interaction as a cause of husband-wife similarities in any of the phenotypes. Only for depression we found a difference between the twin-spouse and parents-correlations, but this did not seem to be explained by duration of marriage. Although longitudinal data would give the best resolution for examining marital interaction, we expect that marital interaction is not the main source of marital resemblance.

Implications

Our study has implications for both psychiatric twin research and clinical practice.
To study genetic and environmental influences on psychiatric orders quantitative genetic models are usually fitted to twin data under the assumption that phenotypic assortment is absent. If phenotypic assortment would exist, a bias is seen depending of the model used: a small upward bias of the genetic variance in an AE model (Neale & Cardon, 1992), i.e., a model with additive genetic (A) and specific environmental (E) influences on psychiatric disorders, and a downward bias of the genetic variance in an ACE model, a model also including shared environmental influences (C). In an AE model the upward bias is small and, depending on the true heritability, amounts up to 3%, for a marital correlation of .2. The downward bias of an ACE model is more substantial. Using a formula to correct C for phenotypic assortment (Martin, 1978), the bias for an ACE model with an estimation of 40% for the proportion of variance explained by A, 20% for C and 40% for E is about 10%, for a marital correlation of .2. This would mean that after correction the proportion of variance explained by A would be 50% and C 10%. In the present study we found only little marital resemblance and even if phenotypic assortment would completely explain this resemblance, the bias in estimates reported in twin studies on psychiatric diagnoses is likely to be very small. Interestingly, if gene-(shared) environment correlation would be present, social homogamy would have consequences for the genetic structure in a population, but as the correlations are small and shared environment does not seem to play a role in the phenotypes of the current research, we expect this not to be a problem.

The spouse correlations we found were not zero, which means that in some couples both partners similarly have anxious, depressed or OC symptoms. It is therefore important to encourage a partner to come along with the patient, not only to have better information of the situation of the patient or discussing the role of the partner in a treatment plan but also to examine if there are psychiatric symptoms present in the partner (Low *et al*, 2007).

Limitations

The results of this study should be interpreted in the light of three possible limitations.

First, for estimating marital resemblance we use information on partners who were still together. In general, the rate of divorce in subjects without interviewed partner is higher. Furthermore psychiatric pathology in divorced pairs is increased (Maes *et al.*, 1998; Wade & Cairney, 2000), which gives a bias in the estimation of marital resemblance. In our sample, it appears that participants who were divorced at least a year before participation and had not met a new partner, showed significantly higher rates of depressive ($F = 98.7$, $p < .001$) and anxious symptoms ($F = 89.1$, $p < .001$) but not of OC symptoms ($F = 3.6$, $p = .06$) compared with pairs who were still together.

Second, in the current study symptoms were measured cross-sectionally. Ideally, to study marital resemblance, partners are followed longitudinally, preferably starting shortly after having met their partner.

Third, although the measurements we used are well-known questionnaires showing satisfying psychometric properties, some limitations regarding these measurements have to be mentioned. First, we measured symptoms, no DSM diagnoses. This hampers the usefulness of the current study in clinical practice and comparability with studies based on DSM diagnosis. Nevertheless, findings from the current study are remarkably comparable with the study of Maes *et al.* (1998), who used DSM-III-R diagnoses. Second, distributions of the measurements used were skewed, which may cause underestimation of correlations. Derks *et al.* (2004) showed that use a threshold model and estimate polychoric correlations could be a solution, but this has the disadvantage of losing power. We therefore chose to use the raw data. Third, the reliability for cross-sectional assessments of symptoms at one point in time is only moderate. Lastly, high intercorrelations were found for the examined traits, ranging from .49 to .71. Although OC, anxious and depressive traits show high comorbidity, the question remains if the intercorrelations are caused by comorbidity or by overlapping instruments. Interestingly, Maes *et al.* (1998) found similar intercorrelations ranging from .58 to .71 for comparable DSM diagnoses like major depression and generalized anxiety disorder. This might suggest that comorbidity could be an important cause of the high intercorrelations we found.

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CHAPTER 6

Heritability of obsessive-compulsive symptoms: a study of twins, sibs and their parents

van Grootheest, D. S., Beem, A. L., van den Berg, S. M., Beekman, A. T., Cath, D. C. & Boomsma, D. I.

Heritability of obsessive-compulsive symptoms: a study of twins, sibs and their parents

van Grootheest, D. S., Beem, A. L., van den Berg, S. M., Beekman, A. T., Cath, D. C. & Boomsma, D. I.

ABSTRACT

Background Evidence from twin studies indicates that genetic and non-shared environmental factors play a significant role in the etiology of variation in obsessive-compulsive (OC) symptoms. Although twin studies are powerful to detect genetic and environmental influences, they do not provide information on the processes of assortative mating and non-genetic parent-offspring transmission.

Methods We examined the role of genetic and environmental factors to variation in OC symptoms using an extended twin design, including 4408 twins, 1309 siblings, and 2305 parents. This design allows to test for genetic and cultural transmission, while taking assortative mating in the parental generation into account. The 12-item Padua Inventory Revised Abbreviated was used to measure OC symptoms.

Results Both additive genetic and non-shared environmental factors contributed significantly to the variance of OC symptoms in men and women. In men, shared environmental influences played a relative large role (explaining 27%) with a small role for genetic factors (1%). Significant influence of cultural transmission was only found for men, but was minimal (<1%). Non-shared factors explained 71% of the variance of OC symptoms. For women, the heritability was estimated at 37% and non-shared environment explained 63% of the total variance in individual differences in OC symptoms.

Conclusions The effect of cultural transmission in OC symptoms is minimal, although a significant contribution of shared environmental factors is found in men. In women there is no contribution of shared environment and familial resemblance is explained by shared genes.

Obsessive-Compulsive Symptoms (OCS) tend to cluster in families (Pauls *et al.*, 1995; Nestadt *et al.*, 2000). The resemblance between relatives can be due to genetic transmission, environmental similarities, cultural transmission from one generation to the next, social interactions between family members, or a combination of these mechanisms. When one wants to study causes of familial resemblance within first-degree relatives, such as parents and their offspring, or siblings reared together, it is not possible to disentangle shared genetic from shared (i.e. family) environmental effects. With a twin design a distinction between genes and shared environment can be made, since monozygotic (MZ; identical) twins share all, or nearly all of their DNA, while dizygotic (DZ) twins share on average 50% of their segregating genes (Plomin *et al.*, 2002; Boomsma *et al.*, 2002a). Therefore, more resemblance between MZ than between DZ twins is suggestive of genetic influences on familial resemblance.

Although adult twin studies have evolved from case-studies with patients with OCD into large samples of unselected subjects using the whole distribution of OC Symptoms (van Grootheest *et al.*, 2005), no study have used the extended parent- twin design yet. Clifford *et al.* (1984) examined 419 twin pairs of monozygotic (MZ) and dizygotic (DZ) twins with the Leyton Obsessional Scale. The heritability of OCS was estimated to be 47%. Another study using unselected adult twins was published by Jonnal *et al.* (2000). They examined 527 female twin pairs and carried out a factor analysis on 20 Padua Inventory items. Two major factors were used in the genetic analysis, one factor which described thoughts and one which described actions, e.g. obsessions and compulsions. Heritabilities of 33% and 26% for obsessions and compulsions, respectively, were found. Recently, van Grootheest *et al.* (2007b) obtained the Young Adult Self Report Obsessive-Compulsive Subscale (YASR-OCS) from a group of 5893 mono- and dizygotic twins, and 1304 additional siblings and found a moderate heritability of 39% for men and 50% for women.

The classical twin design in which data of MZ pairs are compared with data from DZ pairs relies on several assumptions. One of these assumptions entails that the phenotypes of parents of the twins are uncorrelated (i.e., random mating between spouses), and that there is no genotype-environment correlation. Recently, van Grootheest *et al.* (2008) demonstrated that a small but significant correlation exists between parents for OC symptoms, suggesting some degree of non-random mating called phenotypic assortment. If this assortment between parents is not included in the model, a bias with in general small influences on the heritability estimates of OC symptoms is seen, depending on model and height of the estimates. For example, in models with a moderate heritability of 40% and effects of shared environment of 20%, there would be an underestimation of genetic factors and an overestimation of shared environmental factors of about 10%, if a marital correlation of .2 is not included in the model.

By including parents of twins in a twin design, extra information is added about the origins of individual differences. Parent-offspring resemblance may reflect genetic transmission, cultural transmission, or both. In the case of genetic transmission resemblance between parents and offspring is caused by the genes which are transmitted from the parents to their children. In a family design, genetic transmission is confounded with cultural transmission. Cultural transmission refers to the non-random distribution of genotypes over environments and may for instance occur when parents transmit not only their genes but also their environment to their children. Parents may create a particular kind of environment that is correlated with their genotype or their phenotype (van leeuwen *et al.*, 2008), for example, bright parents might stimulate their children with schoolwork, where depressive parents might create a non-stimulating environment. Whenever there is cultural transmission in the presence of genetic transmission, environmental influences become correlated with genetic influences and genotype-environment correlation becomes operant. Both forms of transmission lead to parent-offspring correlations, as well as correlations between siblings and twins who grow up in the same home environment. In the classical twin design genetic and cultural transmission can be distinguished because cultural transmission will increase shared (or common) environmental variance. However, note that significant C does not automatically imply cultural transmission.

In this paper we use an extended twin design which includes MZ and DZ twins and their parents, to study to the heritability of OC symptoms, using a 12-item version of the PI-R (Cath *et al.*, 2008). To maximize statistical power and to test if results generalize to non-twins, the study was extended by including siblings (Posthuma & Boomsma, 2000; Stoel *et al.*, 2006). With this design, heritability can be studied, while taking into account cultural transmission and assortative mating.

METHODS

Participants

This study is part of an ongoing longitudinal survey study of the Netherlands Twin Register (NTR), which has assessed families with adolescent and adult twins roughly every two years since 1991 (Boomsma *et al.*, 2002b; 2006). Each survey, with the exception of the 1995 wave, collected information on personality and psychopathology. Sample selection and response rates are described in detail in Boomsma *et al.* (2002b; 2006). For this study, data of twins, their sibs and their parents from the 2002 survey were used. We received complete surveys for OC symptoms of respectively 4408 twins, 1309 siblings, and 2305 parents. The mean ages of the subjects at the time of the survey were 32.8 years (SD = 11.3) for twins, 35.3 years (SD = 12.3) for the siblings and 56.4 years (SD = 5.9) for the parents of the twins.

Measures

In the 2002 wave of data collection, the 12 item Padua Inventory Revised Abbreviated (PI-R ABBR) was included (Cath *et al.*, 2008), derived from the Padua Inventory-Revised version (PI-R), which is a widely used self report inventory on obsessive-compulsive symptoms. The PI-R is translated into Dutch, revised and validated by Van Oppen *et al.* (1995). The PI-R ABBR is shown in table 1. To investigate its psychometric qualities psychometric analyses have been conducted in three groups (Cath *et al*, 2008) derived from an earlier study by van Oppen *et al.* (1995). Cronbachs' α of the scale was 0.73, which is an indication of good internal consistency. The sensitivity and specificity for the 12 items to detect OCD were .74 and .72 respectively, when comparing a group of OCD patients with clinical controls (Cath *et al.*, 2008). Analyses of Variance (ANOVAs) of PI-R ABBR scores revealed a significant main between-group effect ($p < .0001$). Post-hoc t-tests showed that the mean PI-R ABBR OC score for the OCD group (20.7 ± 8.1) was significantly higher than scores of both the psychiatric (12.4 ± 7.4) and a population control group (6.6 ± 5.6; $p < .0001$ in both comparisons). In table 2 the minimum, maximum and mean scores and SD can be found for the PI-R ABBR for twins, siblings and parents.

Statistical modeling

In the classical twin study, the relative contribution of genes and environment to phenotypic variation is estimated from the comparison of MZ and DZ correlations, or covariances. When DZ twins are as alike as MZ twins, phenotypic variation is caused by shared and unique environment. The more similar MZ twins are relative to DZ twins, the more phenotypic variability is caused by genetic factors. Additive genetic effects (A) represent the additive effects of alleles (possibly at multiple loci), and are assumed to be perfectly correlated in MZ twin pairs, as they have the same DNA sequence. DZ twins and siblings share on average half of their segregating genes; therefore the genetic correlation

Table 1. The 12 items of the PI-R ABBR

	Items	Original Factor
1	In certain situations, I am afraid of losing my self-control and doing embarrassing things	Impulses
2	I check and recheck gas and water taps and light switches after turning them off	Checking
3	I feel obliged to follow a particular order in dressing, undressing and washing myself	Precision
4	When I see a train approaching I sometimes think I could throw myself under its wheels	Impulses
5	I return home to check doors, windows , drawers etc., to make sure they are properly shut	Checking
6	When I start thinking of certain things, I become obsessed with them	Rumination
7	I feel I have to repeat certain numbers for no reason	Precision
8	Unpleasant thoughts come into my mind against my will and I cannot get rid of them	Rumination
9	My thoughts constantly go astray, therefore I find it difficult to attend to what is happening around me	Rumination
10	I sometimes have to wash or clean myself dimply because I think I may be dirty or 'contaminated'	Washing
11	I get upset and worried at the sight of knives, daggers and other pointed objects	Impulses
12	If I touch something which I think is 'contaminated', I immediately have to wash or clean myself	Washing

between their additive genetic values (A) is ½ under random mating. The expectation for parent-offspring genetic correlation is also ½ under random mating. Non-random mating due to phenotypic assortment will lead to an increase in resemblance among siblings and between parents and offspring.

Figure 1 shows a path diagram of the model used in the present research (Fulker, 1982; Boomsma & Molenaar, 1987). The phenotypes of the parents (parent 1 and parent 2) and of their twin offspring (T1 and T2) are represented by squares. The sibling data are omitted from the figure for clarity, but the expectations for twin-sib resemblance are the same as for DZ twin resemblance. Variability in OC symptoms is caused by variation in A and E, and these are represented as latent factors in the model with unit variance. The factor loadings on the latent factors are represented by **h** or **x** (for A, in male and females respectively), and **e** or **y** (for E in male and females). Parents pass their genes to their children, which is represented by arrows going from A of the parents to A of the child, with the factor loading ½. In the children, part of the genetic variance is explained by transmission from the parents. The remaining residual additive genetic variance represents the variance that results from recombination (which is uncorrelated in siblings and correlated unity in MZ pairs).

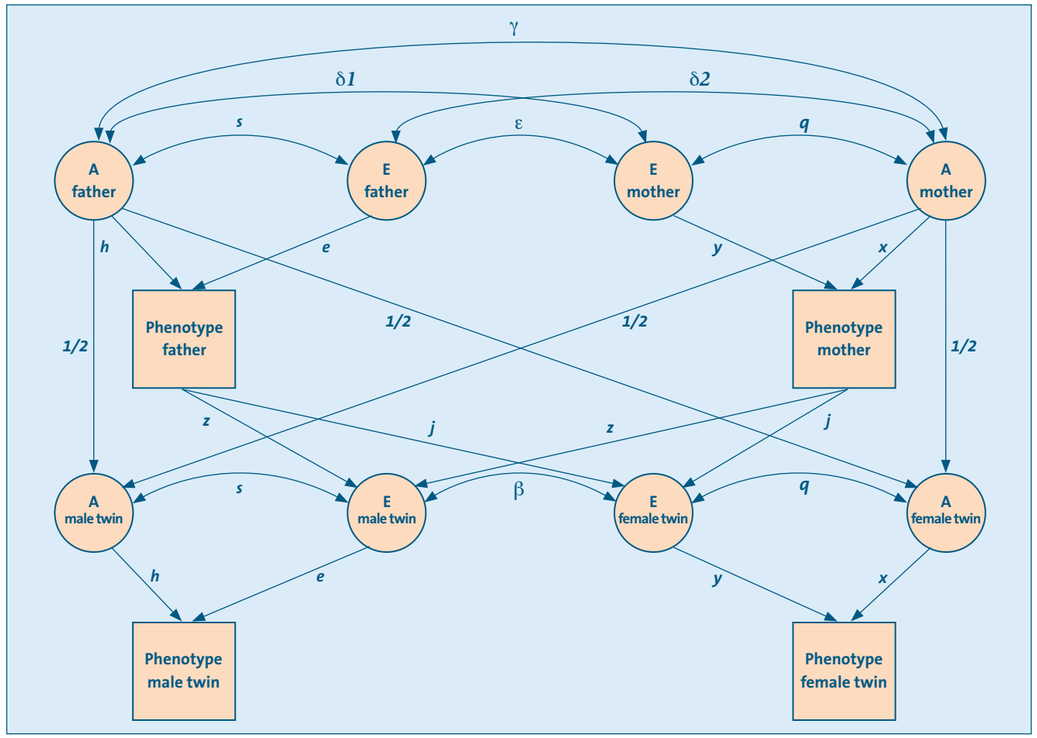
The Greek letters on the top of the diagram in Figure 1 represent the correlations induced by phenotypic assortment. Coefficient **γ** represents the genotypic correlation between the parents, **ε** the environmental correlation between the parents, and **δ*1*/δ*2*** represent the correlations of the environment of one parent with the genotype of the other parent. All three correlations are induced by phenotypic assortment that can be represented as a parameter equal to the spousal correlation. This spousal correlation can be drawn as a co-path (Cloninger, 1980) between the phenotypes of the parents instead of the paths which are represented by the Greek letters. Cultural transmission, i.e. the regression of the child's environment on the parents' phenotypes, is represented by **z** (to male offspring) or **j** (to female offspring). If **z** or **j** is not equal to 0, genotype and environment in the offspring generation become correlated. As negative cultural transmission is unlikely, **z** and **j** had a lower bound of 0. It is assumed that the system is at equilibrium, i.e. s le over generations, implying that genotype and environment are correlated to the same extent in the parents as in the offspring. This GE correlation, **s** (for males) or **q** (for females), is represented by the double-headed arrow between A and E (Eaves *et al.*, 1989). The correlation **β** between the E components represents the residual shared environment within the offspring generation, not caused by cultural transmission, and was estimated for twins and sibs.

Table 2. Estimates of Mean and Standard Deviation (SD) of the sum score of the PI-R ABBR

	N	Min	Max	Mean	SD
Fathers	1045	0	34	8.2	5.2
Mothers	1260	0	38	8.4	5.1
Brothers	481	0	25	8.1	5.0
Sisters	828	0	33	8.2	5.2
Male twins	1406	0	33	7.9	5.6
Female twins	3002	0	47	8.1	5.6

The OC symptom scores were first analyzed by fitting a saturated model to the data from DZ and MZ twin families. This model specifies all correlations between family members, and estimates means and variances. Several assumptions were tested, such as equality of means and variances between MZ and DZ twins and between twins, siblings and parents. Next, a genetic model was fitted to the data. In model fitting procedures, the saturated model is used as a starting-point for the comparison of different, nested models. The fit and parsimony of the various nested models are judged using likelihood ratio tests in which the negative log-likelihood (-2LL) of the nested model is compared with -2LL of the saturated model. Subtracting the two -2LLs from each other yields a statistic that is asymptotically

Figure 1. The psychometric model for multiple raters



Parent-offspring model. A and E represent genotype and environment. γ, ε and δ represent correlations induced by assortative mating. s and q are the correlations between A and E for male and female respectively. Influence of parental phenotype on child's environment is z (if to son) or j (if to daughter), and residual shared environment among offspring is β. h and y represent genetic factorloadings for men and women respectively, e and x represent environmental factorloadings for men and women respectively

distributed as χ^2 with degrees of freedom (df) equal to the difference between the number of parameters in the two models. All models were tested in the statistical modelling package Mx (Neale *et al.*, 2003). Each model in the model fitting sequence was evaluated at a significance level of .01.

RESULTS

Working from a fully saturated model, there were no sex-differences in means ($\chi^2(1.9) = (1)$, $p = .17$) and variances ($\chi^2(.5) = (1)$, $p = .48$). MZ twins had the same variances as DZ twins across sexes ($\chi^2(11.4) = 5$, $p = .04$). The mean scores (see table 2) could be constrained to be equal for twins, sibs and parents ($\chi^2(5.1) = (2)$, $p = .08$). The variances across sibs and parents was equal (total variance of 26.5) ($\chi^2(0) = (1)$, $p = .99$), but the variance in twins was slightly larger (total variance of 31.1) ($\chi^2(24.3) = 1$, $p < .01$). This difference in variances was taken into account in subsequent analyses.

The twin-sib, DZ twin-DZ twin and sib-sib correlations could be constrained to be equal for males ($\chi^2(1.9) = 2$, $p = .39$), females ($\chi^2(1.1) = 2$, $p = .58$) and opposite sex pairs ($\chi^2(3.9) = 2$, $p = .14$). The correlations based on the constrained model are shown in Table 3. For women the MZ twin correlation was more than twice the combined DZ/sib correlation. Therefore, we chose to fit an AE model for women. For men, the MZ correlation is less than twice the combined DZ/sib correlation, indicating that shared environmental effects may play a role in individual differences in OC symptoms, besides additive genetic effects. We decided to fit an ACE model for men, i.e., we estimated β, the correlation between E, only for men. Correlations for parents and offspring are of the same order of magnitude as the DZ-FF and DOS correlations and may point to both genetic and cultural inheritance. Finally we observed a significant correlation between scores of spouses (0.17) which was modelled as the result of phenotypic assortment (Van Grootheest et al, 2008)

The results of genetic analyses are summarized in Table 4. An ACE model for men and AE model for

Table 3. Twin, twin-sib, parent and parent-child correlations for the PI-R ABBR

MZM	DZM/ sibsMM	MZF	DZF/ sibsFF	DOS/ sibsOS	Parents	Father-son	Father-daughter	Mother-son	Mother-daughter
.37	.28	.44	.14	.09	.17	.17	.07	.18	.12

MZM, monozygotic males; MZF, monozygotic females; DZM, dizygotic males; DZF, dizygotic females; DOS, dizygotic opposite sex; sibsMM, brothers; sibsFF, sisters; sibsOS, sibs of opposite sex

women describes the data adequately when compared with the fully saturated model (model 1). There was no significant contribution of cultural transmission for women, but we found cultural transmission for men (model 3). There was a significant spousal correlation (model 4). Shared environmental factors (C) for men also appeared to be significant (model 5). Furthermore, genetic influences were significant for men (model 6) and women (model 7) and could not be dropped without a significant deterioration in fit.

The best-fitting model (model 3) estimated the heritability of OC symptoms for men at 1%, the effect of cultural transmission and gene-environment correlation at less than 1%, shared environmental effects at 27% and non-shared environmental effects at 71%. For women, the heritability was estimated at 37% and non-shared environment explained 63% of the total variance in individual differences in OC symptoms.

If the found shared environmental influences for men are not a coincidental finding, one wonders what causes these shared environmental influences. These influences can arise from non-parental sources, special twin environment and cultural transmission (i.e., parental influences). We could not find evidence for a special twin environment as we could equal DZM, twin-sibM and sibM-sibM correlations, but did find evidence for significant cultural transmission. However, the variation explained by cultural transmission is minimal and the remaining nonshared environmetal influence large. This would imply that the shared environmental influences would be caused by non-parental sources like co-twins, sibs and peer groups. A well-known example of within generational influences is found for smoking, where the association between smoking behavior in parents and their children can be most likely accounted for by their genetic relatedness. The idea of social learning in smoking

Table 4. Model fitting results using the PI-R ABBR

Number of model	Type of model[a]	-2LL	χ^2	df	p	Compared with model
1	Fully saturated model	49279.5	-		-	-
2	ACE model for males and AE for females	49437.0	157.5	196	.98	1
3	**Model 2 + no cultural transmission for women**	**49437.0**	**0.0**	**1**	**.99**	**2**
4	Model 3 + no cultural transmission for men	49452.6	15.6	1	<.01	3
5	Model 3 + no C for males	49467.4	30.4	1	<.01	3
6	Model 3 + no A for males	49503.5	66.5	1	<.01	3
7	Model 3 + no A for females	49568.1	131.1	1	<.01	3

[a] A=additive genetic effects; D=dominant genetic effects; C=common or shared environmental effects; E= nonshared or individual-specific effects

DISCUSSION

Results of our analyses extend previous evidence on the contribution of genetic and environmental factors on OC symptoms. Conform earlier research, both additive genetic and non-shared environmental factors appear to contribute significantly to the variance of OC symptoms in males and females. However, in males, shared environmental influences play a relative large role with a small role for genetic factors. In the few studies published on twin studies of OC symptoms in adults, no influence of shared environmental influence was found (Clifford *et al.*, 1984; Jonnal *et al.*, 2000; van Grootheest *et al.*, 2007b). In children and adolescents, where we rather would expect the influence of shared influences, only at age 12 shared influences were found (Hudziak *et al.*, 2004; van Grootheest *et al.*, 2007a). In the future, we will receive new twin data on the PI-R ABBR, which makes it possible to replicate the current findings.

may apply to siblings or peers but does not appear to apply to children learning by modelling from their parents (Maes *et al.*, 2006).

As expected we found a significant influence of assortative mating, but because of the low spousal correlations, the bias in estimates causes by these correlations is minimal (van Grootheest *et al.*, 2008). Together with the finding of a minimal effect of cultural transmission, and thus gene-environmental correlation, and the finding of Jonnal *et al.* (2000), who concluded that the equal environment assumption for OC symptoms was not violated, the assumptions for twin design are met. It furthermore appears that adding the parental data to the twin design does not provide much additional information for this phenotype. Note that the present design is not suited to uncover gene-environment correlations other than resulting form simultaneous genetic and cultural transmission (i.e., passive gene-environmental correlations). Evocative gene-environmental correlation,

where individuals are reacted to on the basis of their genetically influences phenotype, or an active gene-environment correlation, where individuals seek or create environments correlated with their genetic backgrounds.

The results of this study should be interpreted in the context of several potential limitations. First, although the PADUA-ABBR showed a moderately high sensitivity and specificity in diagnosing DSM OCD (Cath *et al.*, 2008), the genetic and environmental contributions presented in this report reflect OCS scores, not clinical measures of DSM-IV OCD. Because of the relatively low prevalence of OCD, twin studies rely on dimensional measures with the underlying assumption that OCD reflects the end of a normal distribution, while OC symptoms represent a milder form of the latter (Jonnal *et al.*, 2000; van den Oord *et al.*, 2003; Kendler, 2005).

Second, the PADUA-ABBR showed a skewed distribution. One could use a threshold model to deal with this problem, but the disadvantage of a threshold model is the loss of power (Derks *et al.*, 2004). Therefore, we decided to use the continuous scales with the disadvantage of possibly underestimating the twin correlations, resulting in underestimating the genetic proportions and overestimating the nonshared proportions a bit.

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PART III. GENETIC AND ENVIRONMENTAL INFLUENCES ON OCS OVER TIME

CHAPTER 7

Genetic and environmental contributions underlying stability in childhood obsessive-compulsive behavior

van Grootheest, D. S., Bartels, M., Cath, D. C., Beekman, A. T., Hudziak, J. J. & Boomsma, D. I. (2007) Genetic and environmental contributions underlying stability in childhood obsessive-compulsive behavior. *Biol Psychiatry*, 61, 308-315.

Genetic and environmental contributions underlying stability in childhood obsessive-compulsive behavior

van Grootheest, D. S., Bartels, M., Cath, D. C., Beekman, A. T., Hudziak, J. J. & Boomsma, D. I.

ABSTRACT

Background Little is known about the stability of obsessive-compulsive (OC) behavior during childhood. The objective of this study is to determine the developmental stability of pediatric OC behavior and the genetic and environmental influences on stability in a large population-based twin sample.

Methods Maternal and paternal ratings on the 8-item Obsessive Compulsive Scale of the Child Behavior Checklist (CBCL-OCS) on Dutch mono- and dizygotic twin pairs from 8083 families were collected at ages 7, 10, and 12 years. Using a longitudinal twin design, stability of OC behavior and genetic and environmental influences on stability were determined. Using cut-off criteria, persistent, resilient, and new onset cases were identified in this sample.

Results OC behavior assessed by the CBCL-OCS showed a moderate stability with phenotypic correlations of around .50 for boys and for girls. Stability of OC behavior was influenced by genetic factors, by environmental factors shared by children growing up in the same family and by non-shared environmental factors. Stability for OCS was lower when categorical data were analyzed, than when quantitative definitions were used.

Conclusions OC behavior is moderately stable in childhood. Stability of OC behavior is influenced by genetic, shared and non-shared environmental factors.

Given how common and impairing obsessive-compulsive disorder (OCD) is in children (Piacentini *et al.*, 2003), a better understanding of the etiology and course of OCD is important. One of the factors that limits a clear understanding of the etiology and development of pediatric OCD is the scarcity of epidemiological studies. Recently, a useful screening measure was developed to identify children at risk for OCD in the population, the Child Behavior Checklist Obsessive-Compulsive Scale (CBCL-OCS) (Nelson *et al.*, 2001). Hudziak *et al.*, (2006) used the CBCL-OCS to determine the prevalence of OCD in US and Dutch population twin samples. They found higher prevalence rates than previously reported. Genetic contributions (Hudziak *et al.*, 2004) accounted for at least 50% of individual differences in CBCL-OCS scores in children at ages 7, 10 and 12. These heritabilities are in line with those from family studies, indicating that childhood onset OCD is highly familial (Pauls *et al.*, 1995; Nestadt *et al.*, 2000; Delorme *et al.*, 2005; do Rosario-Campos *et al.*, 2005).

These data provided an epidemiologic perspective on prevalence and genetic architecture of CBCL-OCS, but did not examine stability and its underlying etiology. Knowledge about persistence, resilience, and new onset cases provides a framework to answer key clinical questions such as: If my child meets CBCL-OCS criteria for OCD at age 7, will (s)he continue to have OCD at age 12? If my child does not meet CBCL-OCS criteria at age 7, what are the odds that (s)he will meet these criteria at a later age? Although genetic and unique environmental influences account for the expression of OC symptoms at any given age, it is unknown which factors account for persistence.

To date, research on persistence of OCD has concentrated on subjects who are patients. A recent meta-analysis on the long-term outcome of pediatric OCD, mostly adolescents, with 521 participants from 16 different study samples, found a persistence rate of 41% for full OCD and 60% including subthreshold OCD (Stewart *et al.*, 2004). Only two of the study samples in this meta-analysis were community samples (Berg *et al.*, 1989; Valleni-Basile *et al.*, 1996). To our knowledge, no previous study has investigated persistence of OCD or OC symptoms in a community sample of children in a younger age group.

The purpose of the present study was to gain insight into stability of CBCL-OCS scores and the etiology of this stability. Longitudinal data were analyzed from twin families in which both parents had rated OC behavior in 7, 10 and 12 year old twins. An advantage of a design in which multiple raters assess the behavior of genetically related subjects (i.e. twins) is that a distinction can be made between variance that is explained by a common perception of the parents (i.e. common phenotype) and variance that is explained by a unique perception of each parent on the behavior of their child (i.e. unique or rater specific phenotype). The common perception is not confounded by rater bias, e.g. the tendency of an individual rater to consistently over- or underestimate scores (Hewitt *et al.*, 1992), or measurement error. The unique phenotype leaves room for specific views of a certain rater, but may include both rater bias and measurement error. We sought answers to the following questions:

1. What is the stability of OC behavior in children over time?
2. To what extent do early cases remit, do new cases emerge, and do other cases persist?
3. To what extent do genetic or environmental influences account for stability of OC behavior?

METHODS AND MATERIALS

Subjects and procedure

The study is part of a longitudinal twin study on emotional and problem behavior in the Netherlands. The subjects are all registered with the Netherlands Twin Registry (NTR), established by the Department of Biological Psychology at the Vrije Universiteit in Amsterdam (Boomsma *et al.*, 2002a). For this study, we included 7-year-old twin pairs from birth-cohorts 1986 - 1996, 10-year-old twin pairs from cohorts 1986 - 1993 and 12-year-old twin pairs from cohorts 1986 - 1990. Both parents were asked to complete a Child Behavior Checklist (CBCL) (Achenbach 1991). Parents who did not return the forms within 2 months received a reminder. If finances permitted, persistent non-responders were contacted by phone. Families who did not participate at one age of the twins could enter the study again at subsequent ages. Among those who received a questionnaire, response rates were 66% at age 7, 64% at age 10, and 64% at age 12. From the original sample, 208 families were excluded because either one or both twins had a disease or handicap that interfered severely with daily functioning at age 12 or younger. The total sample consists of 8083 twin families. Table 1 shows the numbers of maternal and paternal reports on the CBCL-OCS per zygosity and age. Ratings from both parents were available for 5433 twin pairs at age 7, 3172 pairs at age 10 and 1787 pairs at age 12. Maternal ratings were available for 1857, 1217 and 558 twin pairs at ages 7, 10 and 12 respectively. For a small number of twin pairs, only father ratings were available, respectively 92, 74 and 40 twin pairs at age 7, 10 and 12. For mother ratings, 1852 twin pairs participated at age 7, 10 and 12, 1970 twin pairs at age 7 and 10, 144 twin pairs at age 7 and 12 and 224 twin pairs at age 10 and 12. For father ratings, 1338 twin pairs participated at age 7, 10 and 12, 1367 at age 7 and 10, 160 twin pairs at age 7 and 12 and 182 twin pairs at age 10 and 12.

To examine the effects of sample attrition, data from twins who participated three times were compared to data from twins who participated at age 7, but whose parents did not return the CBCL at age 10 and 12. Equal numbers of drop-out were observed for boys and girls. For girls, there were no differences in means between these groups. For boys, the non-response group showed somewhat larger means in CBCL-OCS at age 7. These differences in means were significant, but small (< one standard deviation). Any effect of sample attrition on the results at ages 10 and 12 are accounted for by inclusion of all available data in the analyses, irrespective of the number of times that a family participated.

Zygosity was based on DNA or blood group polymorphisms for 1258 same-sex pairs. For the remaining same-sex twin pairs, zygosity was determined by questionnaire items about physical similarity and frequency of confusion of the twins by family and strangers (Rietveld *et al.*, 2000).

Table 1. Sample sizes (N), means (M) and standard deviations (SD) for CBCL-OCS in 7, 10 and 12-year-old twins by zygosity and rater

	Mother ratings			Father ratings		
	N	M	SD	N	M	SD
7-year-olds						
mzm	1215	.84	1.23	927	.60	.98
dzm	1230	.99	1.42	940	.77	1.20
mzf	1394	.91	1.36	1061	.67	1.11
dzf	1156	1.08	1.55	856	.75	1.21
dos mf	1186	.88	1.38	912	.66	1.08
dos fm	1109	.90	1.31	829	.65	1.05
10-year-olds						
mzm	745	.89	1.27	573	.70	1.05
dzm	680	1.11	1.68	487	.76	1.19
mzf	907	1.05	1.47	666	.78	1.21
dzf	655	1.16	1.66	484	.87	1.41
dos mf	730	.98	1.53	535	.73	1.20
dos fm	672	.99	1.46	501	.74	1.11
12-year-olds						
mzm	422	.86	1.41	329	.64	1.15
dzm	378	1.01	1.69	284	.85	1.39
mzf	494	.92	1.27	385	.65	1.03
dzf	351	.88	1.39	280	.86	1.47
dos mf	370	.89	1.45	288	.62	1.10
dos fm	330	.76	1.20	261	.60	1.04

Mzm, monozygotic male; dzm, dizygotic male; mzf, monozygotic female; dzf, dizygotic female; dos mf, dizygotic opposite-sex twin pairs with male first-born; dos fm, dizygotic opposite-sex twin pairs with female first-born.

Measures

The Child Behavior Checklist (CBCL) (Achenbach 1991; Verhulst *et al.*, 1996) is a widely used questionnaire for parents. It includes 120 items about problem behaviors exhibited by the child over the previous 6 months. The parents respond on a 3 point scale (0 if the item is not true of the child, 1 for sometimes true, and 2 if the item is often true). The characteristics and

psychometric stability of the CBCL have been well established (Achenbach 1991; Verhulst *et al.*, 1996). OC behavior was measured using the CBCL Obsessive-Compulsive Scale (CBCL-OCS) (Nelson *et al.*, 2001). A numerical value for the OCS scale is created by summing the scores on the 8 relevant items, creating a range between 0 and 16. Using a cut-off score of 5 on the CBCL-OCS, 91% of all DSM-determined OCD cases were identified in a clinical sample with reasonable specificity (67.2%) (Hudziak *et al.*, 2006). The cut-off of 5 is used in this study to screen for OCD cases. The CBCL-OCS has been validated in several samples (Geller *et al.*, 2006; Storch *et al.*, 2006).

STATISTICAL ANALYSES

Descriptives and correlations

Means, standard deviations and the effects of sex, rater and zygosity on mean scores were estimated and evaluated with the statistical software program Mx (Neale *et al.*, 2003). Differences in means were tested by likelihood-ratio tests. These tests were performed while taking into account the dependency that exists between scores of the twins. The p-level was set at .01. To get a first impression of the underlying sources of variance and stability of the CBCL-OCS, Mx was used to calculate within-person longitudinal correlations (phenotypic stability of CBCL-OCS), within person inter-parent correlations (parental agreement), twin correlations (cross-sectional twin 1- twin 2 correlations) and, cross-twin-cross-age correlations (e.g. twin 1 at age 7 with twin 2 at age 10). Further, to take rater differences into account, cross-rater twin correlations within age and across age were estimated. Cross-correlations between mother ratings of oldest twins with father ratings of youngest twins, or the other way around, form the basis for the decomposition of the variance into a part on which both raters agree and a part on which they disagree. The cross-rater twin correlations over time (the cross-twin-cross-age-cross-rater correlations) are used to investigate the underlying developmental patterns of the distinct common and rater specific variance components.

Genetic Modeling

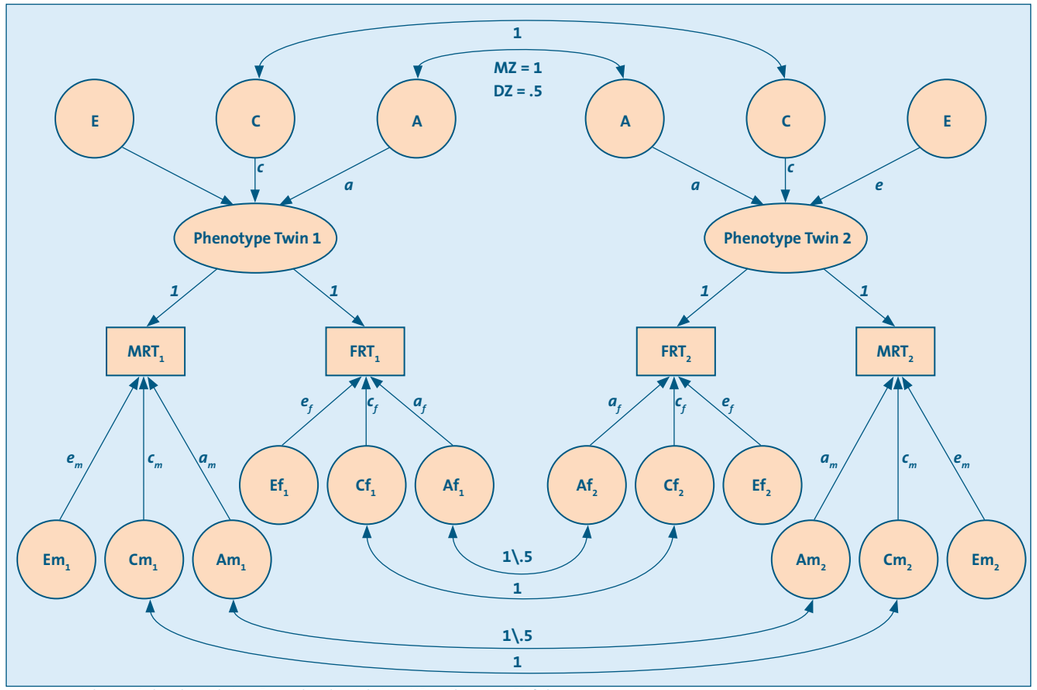
In the classical twin design the relative contributions of genetic and environmental factors to individual differences in OCS scores can be inferred from the different levels of genetic relatedness between MZ and DZ twins. Individual differences may be due to additive genetic (A), shared environmental (C) or non-shared environmental (E) factors (Boomsma *et al.*, 2002b). Additive genetic factors are correlated 1.0 in MZ twins, since MZ twins are genetically identical. For DZ twins, the additive genetic factors are correlated .5, because DZ twins share on average half of their segregating genes. The environment shared by a twin pair is assumed not to depend on zygosity, and thus shared environmental factors correlate 1.0 in both MZ and DZ twins. E or non-shared environment is by definition uncorrelated. All uncorrelated error is also absorbed in the E term.

To model the ratings from two parents for each twins, we used a psychometric model (see figure 1) (Bartels *et al.*, 2003; Bartels *et al.*, 2004a; Hewitt *et al.*, 1992) and expanded this model to longitudinal data. The psychometric model allows the parental ratings to be influenced by aspects of the child's behavior perceived commonly by both parents (the common or rater independent phenotype) and by aspects of the child's behavior that are perceived uniquely by each parent (the unique or rater-specific phenotype). In this model, both the variation of the rater-independent and rater-specific aspects can be influenced by genetic, shared environmental and non-shared environmental factors. The common phenotype represents the part of behavior similarly assessed by both parents and can be considered as independent of rater bias and unreliability of the ratings. Unique perceptions of the child's behavior can arise if the child behaves differentially towards the parents or if the parents observe the children in different situations. By testing the significance of genetic effects on the unique phenotype, it can be established whether the raters must have been assessing a "real" but unique aspect of the child's behavior. Error and\or unreliability do not cause systematic effects and cannot mimic genetic influences. The shared environmental effects on the unique phenotype may be confounded by rater bias, such as using normative standards or response styles. Because rater bias is independent of zygosity, it mimics shared environmental effects. A further advantage of the longitudinal psychometric model is that genuine unique non-shared environmental effects can be distinguished from random measurement error. Random errors of measurement are age specific and are unlikely to contribute to the correlations across time in non-shared environmental effects.

To expand the psychometric model to a longitudinal design we used a Cholesky or triangular decomposition. This decomposition is descriptive and not driven by a specific developmental hypothesis. It decomposes a covariance matrix into genetic and non-genetic covariance matrices and may be used to obtain genetic and environmental correlations across time in longitudinal datasets.

We tested whether the model could be simplified by dropping one or more latent factors. The rater-specific non-shared environmental (E) factor was never dropped from the model, because in addition to non-shared environmental experiences, this factor includes measurement error. The models were fitted to raw data with Mx (Neale *et al.*, 2003), by the method of raw maximum likelihood estimation. This allowed the use of all twin data, whether or not there were missing parental ratings at certain time points. Goodness-of-fit was assessed by likelihood-ratio chi-square tests. These tests compare the differences between -2-log likelihood of a full model with a restricted nested model. This difference is distributed as an X^2, and the degrees of freedom (df) for this test are equal to the difference between the number of estimated parameters in the full model and that in the restricted model. A large X^2 value in comparison to the number of df suggests that the simpler model does not fit the data as appropriately as the more complex model. More technical details of genetic model-fitting analyses are reviewed elsewhere (Neale and Cardon 1992).

Figure 1. The psychometric model for multiple raters



A, genetic contribution; C, shared contribution; E, non-shared contribution; MR, mother rating; FR, father rating.

RESULTS

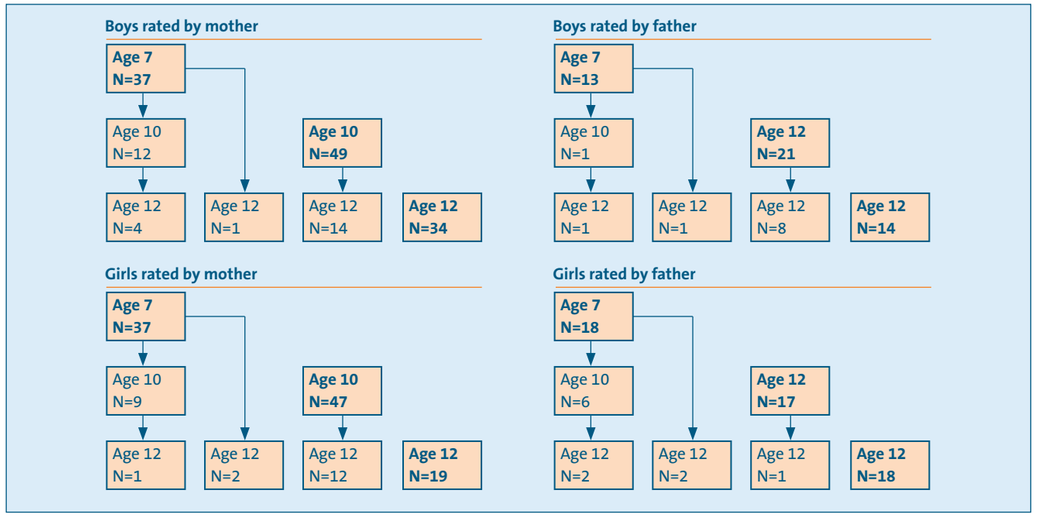
Descriptive statistics

Table 1 summarizes the means and standard deviations for the CBCL-OCS by age and sex in mother and father reports. Mothers reported significantly more OC symptoms than fathers for both boys and girls, except for female DZ twins at age 12 ($\Delta\chi^2(1) = .50$, $p = .48$). No significant differences were seen between boys and girls. No differences between zygosity groups were found with the exception of age 7. At that age, DZ female twins had significantly ($\Delta\chi^2(1) = 7.78$, $p < .01$) more OC-symptoms than MZ female twins according to mother ratings and DZ male twins had higher means than MZ male twins according to father ratings ($\Delta\chi^2(1) = 9.65$, $p < .01$).

Persistence of cases of OCD

Table 2 shows persistence of cases with a CBCL-OCS score of 5 or higher. It is clear that the stability of cases meeting cut-point criteria for pediatric OCD is low. Most cases had a score of 5 or higher at one specific age only. When using a categorical approach such as this, we can identify cases of persistence, remission, and new-onset. For example, for boys rated by mother, only four cases had a score of 5 or higher at all three ages. These data shed light on computing stability according to diagnostic cutpoints, versus using quantitative computations as below. The lower mean CBCL-OCS scores of fathers (see descriptive statistics) is reflected in the fact that cases rated by mother outnumber cases rated by father. Interestingly, using a cutoff of 4 for fathers gave almost exact the same pattern (not shown) as for mothers, using a cutoff of 5.

Table 2. Cases with score of 5 or higher on the CBCL-OCS at different ages



Bold faced numbers show the number of new cases of OCD at that specific age. Non-bold numbers show the cases which persist at a specific age. For example, boys rated by mother: of the 37 cases at age 7, 12 cases persisted at age 10 of which 4 persisted at age 12. The case from age 7 which showed up at age 12, had a score lower than 5 at age 10.

Correlations

Table 3 contains the within-person phenotypic correlations over time. These correlations provide an indication of the stability of the expression of CBLC-OCS, irrespective of possible changes in group means. Both boys and girls displayed a comparable degree of stability of about .50 from ages 7 to 10 and from ages 10 to 12 for both mother and father ratings. Within-person inter-parent correlations were comparable over the distinct zygosity groups and at the distinct ages (not shown). The correlations ranged between .48 and .73 with an average of .58.

Table 4 presents cross-sectional twin correlations (diagonal) for MZ and DZ pairs. MZ correlations are higher than DZ correlations, suggesting genetic influences. MZ correlations were lower than one, which suggests influences of non-shared environment. Further, shared environmental influences were implied by the fact that the MZ correlations are less than twice the DZ correlations.

Twin correlations over time (cross-twin-cross-age correlations) are given on the off-diagonal of table 4. These correlations are informative with respect to the proportion of longitudinal covariance explained by genes and environment for CBCL-OCS over time. Across-age MZ correlations were higher than DZ correlations, with a larger difference for mother ratings, suggesting that additive genetic effects are more important in phenotypic stability of mother ratings compared to father ratings.

Table 5 shows the cross-twin-cross-rater correlations within age (diagonal) and across age (off-diagonal). The cross-twin-cross-rater correlations give a first indication of the involvement of genes and environmental factors on the common parental view. At all ages, the within age MZ cross-rater correlations were larger than the DZ cross-rater correlations and suggested genetic influences on the common parental phenotype (diagonal). Especially at older ages, the DZ cross-rater twin correlations seemed to be larger than expected on the basis of genetic influences alone, and therefore shared environmental influences seemed to contribute to the common parental phenotype. For each age, the cross-twin-cross-rater correlations were lower than the within rater twin correlations (see table 4, diagonal). The differences indicate the part which is unique to a particular rater (i.e. the unique or rater-specific phenotype). A same pattern of higher MZ than DZ correlations is seen for the cross-twin-cross-rater-cross-age twin correlations (off-diagonal), indicating genetic influences on the stability of the common parental phenotype. The differences between the within rater twin correlations over time (table 4, off-diagonal) were quite small, which means a relatively small influence of the unique or rater-specific phenotype on stability compared to the larger influence of the common phenotype.

Table 3. Phenotypic correlations for mother and father ratings. Correlations for boys and girls are reported below and above diagonal respectively.

	Mother ratings			Father ratings		
age	7	10	12	7	10	12
7	1	.55	.47	1	.53	.44
10	.55	1	.58	.51	1	.52
12	.43	.58	1	.44	.54	1

girls and boys and between 51% and 62% between age 10 and 12 for both boys and girls for father ratings. The rater-specific phenotype explains the rest of the covariance and became more important with increasing age.

Table 4. Within age twin correlations (diagonal) and across-age twin correlations (off-diagonal) by sex and zygosity for mother and father ratings. Correlations for boys and girls are reported below and above diagonal respectively.

		Mother ratings of the oldest			Father ratings of the oldest		
	age	7	10	12	7	10	12
youngest				MZ			
	7	.56\.56	.30	.26	.58\.56	.37	.25
	10	.38	.59\.53	.36	.31	.51\.49	.32
	12	.27	.32	.55\.52	.24	.31	.43\.50
				DZ			
	7	.29\.29	.18	.13	.32\.29	.20	.19
	10	.22	.34\.32	.20	.22	.31\.33	.31
	12	.21	.21	.28\.35	.21	.20	.29\.39
				DOS*			
	7	.28\.34	.23	.12	.30\.34	.20	.14
	10	.19	.35\.34	.13	.18	.28\.32	.32
	12	.20	.27	.39\.25	.09	.16	.26\.39

* Dizygotic opposite-sex twin pairs with male first-born below diagonal; Dizygotic opposite-sex twin pairs with female first-born above diagonal.

GENETIC MODELING

Rater (Dis)agreement of OC behavior

Table 6 gives the percentages of the genetic, shared and non-shared environmental contributions to the variances (diagonal) and covariances across time (off-diagonal) of the CBCL-OCS for the common phenotype and the rater-specific phenotype based on the longitudinal analyses for boys (below diagonal) and girls (above diagonal). In table 6, common and unique variance or common and unique covariance add up to 100%. There were no influences from C on rater-specific ratings, ($\Delta\chi^2(24) = 11.89$, $p = .98$). The influence of common family environment (C) on the common phenotype was significant. The influence of additive genes (A) was significant for both the common and the rater-specific phenotype.

As can be seen in table 6, for mother ratings at age 7, the variance explained by the total common phenotype explained almost half of the total variation, and this is decreasing to roughly 30% at the age of 10 and 12. The remaining variation was rater specific. For father ratings, the total common phenotype explained almost 60% of the variance at age 7 and 40% of the variance at age 12. In other words, parental agreement decreased when children grew older.

For stability (off-diagonal covariances), we see the same pattern with a decrease in parental agreement when children grew older. For example, the total covariance of the common phenotype varied between 65 and 81% between age 7 and 10 for mother ratings for both

Table 5. Cross-twin-cross-rater correlations within age (diagonal) and across age (off-diagonal) by sex and zygosity. Correlations for boys and girls are reported below and above diagonal respectively.

		Mother ratings of the oldest		
	age	7	10	12
Father ratings of th e youngest			MZ	
	7	.31\.30	.25	.20
	10	.21	.30\.27	.21
	12	.21	.25	.27\.24
			DZ	
	7	.15\.12	.13	.11
	10	.13	.17\.18	.16
	12	.17	.13	.15\.15
			DOS*	
	7	.12\.15	.12	.08
	10	.11	.14\.12	.13
	12	.09	.11	.16\.11

* Dizygotic opposite-sex twin pairs with male first-born below diagonal; Dizygotic opposite-sex twin pairs with female first-born above diagonal.

Underlying resources of stability of OC behavior

Table 7 gives the percentages of variance explained by genetic influences (A), environmental influences shared by twins (C) and non-shared environment (E). These are given for the total variance (diagonal; shaded cells) and total covariance (i.e. stability; off-di-

Table 6. Percentages of the genetic (A), shared (C) and non-shared (E) environmental contributions to the total variances (diagonal; bold) and covariances (off-diagonal) of the CBCL-OCS for the common phenotype and the unique/rater-specific phenotype based on the Cholesky decomposition model for boys (below diagonal) and girls (above diagonal). Note that common and unique phenotype add up to 100%.

		Mother ratings			Father ratings		
	age	7	10	12	7	10	12
Total common phenotype	7	46\42	67	78	59\56	77	100
	10	65	30\32	52	81	42\42	62
	12	82	42	30\36	98	51	39\44
A_c [a]	7	**26\21**	30	27	**33\28**	34	35
	10	35	**15\12**	14	44	**21\16**	16
	12	36	16	**4\3**	43	19	**5\4**
C_c [b]	7	**10\11**	18	39	**13\15**	21	50
	10	13	**6\9**	30	16	**8\12**	36
	12	38	22	**26\31**	46	27	**33\38**
E_c [c]	7	**10\10**	19	12	**13\13**	22	15
	10	17	**9\11**	8	21	**13\14**	10
	12	8	4	**0\2**	9	5	**1\2**
Total unique phenotype	7	54\58	33	22	41\44	23	0
	10	35	70\68	48	19	58\58	38
	12	18	58	70\64	2	49	61\56
A_u [d]	7	**27\28**	10	0	**26\26**	0	0
	10	22	**43\34**	22	0	**27\26**	0
	12	18	27	**31\29**	0	0	**12\26**
E_u [e]	7	**27\30**	23	22	**15\18**	23	0
	10	13	**27\34**	26	19	**31\32**	38
	12	0	31	**39\35**	2	49	**49\30**

[a] Additive genetic influence on the common phenotype; [b] shared environmental influence on the common phenotype; [c] non-shared environmental influence on the common phenotype; [d] Additive genetic influence on the unique phenotype; [e] non-shared environmental influence on the unique phenotype.

Table 7. Percentages of the genetic (A), shared (C) and non-shared (E) environmental contributions to the total variance (diagonal; bold) and total covariance (off-diagonal) of the CBCL-OCS for boys (below diagonal) and girls (above diagonal). Common phenotype and unique/rater-specific phenotype have been added together.

		Mother ratings			Father ratings		
	age	7	10	12	7	10	12
A	7	**53\49**	40	27	**59\46**	34	35
	10	57	**58\46**	36	44	**48\42**	16
	12	54	43	**35\32**	43	19	**17\30**
C	7	**10\11**	18	39	**13\15**	21	50
	10	13	**6\9**	30	16	**8\12**	36
	12	38	22	**26\31**	46	27	**33\38**
E	7	**37\41**	42	34	**28\31**	45	15
	10	30	**33\45**	34	40	**44\46**	48
	12	8	35	**39\37**	11	54	**50\32**

Common phenotype and unique/rater-specific phenotype have been added together.

agonal) of the CBCL-OCS, the common phenotype and rater-specific phenotype have been added together.

For boys, analyses of the covariance showed that stability could be largely explained by additive genetic influences, 51% (57 + 54 + 43 / 3) for mother ratings and 35% (44 + 43 + 19 / 3) for father ratings, on average. The differences for father and mother ratings are mainly explained by the fact that fathers do not add any unique additive genetic information on stability (see table 6), while mothers do, especially for boys. For girls, stability could be explained by additive genetic influences of 34% for mother ratings and 28% by father ratings. For girls, genetic, shared environmental and non-shared environmental influences explained each for a third of the stability of OC behavior.

Same or different genes across ages?

Analyses of the covariance similarly assessed by both parents (the common phenotype), showed, that stability could be partly explained by common additive genetic influences, 43% of the covariance on average for boys and 35% for girls (not shown). Interestingly, a closer look on the parameter estimates in Mx revealed that the genetic influences seen on the common phenotype at ages 10 and 12 are transmitted from age 7, so one underlying set of genes can be considered to be of importance for OC behavior between age 7 and 12.

DISCUSSION

This is the first longitudinal twin study of stability of OCS in children from ages 7 to 12. It has focused on stability of childhood OC behavior and on the underlying etiology of this stability. By using both maternal and paternal ratings with large sample sizes we could examine differences between mothers and fathers in the ratings of their children, identify that aspect of the phenotype that both parents agree upon, and identify possible rater bias. Several important findings emerged that are relevant to both clinical practice and future research.

What is the stability of OC behavior in children over time?

In comparison with other phenotypes, OC behavior showed a moderate degree of stability of .50. Bartels *et al.* (2004b) found a mean phenotypic correlation over time of about .60 for internalizing problem behavior and Rietveld *et al.* (2004) showed a high stability of .70 for attention problems for children in the same age-range. Our result seems to be in line with the result of Stewart *et al.* (2004). They found a persistence rate of OCD of 26% within two community studies included in their meta-analysis, with adolescents only. Thus, having OC behaviour as a child does not automatically imply OC behaviour for the rest of your life. This is also in line with the notion that the prevalence of OCD in children is similar to prevalence rates in adults, which means, as only one-third to one-half of adults with OCD develop the disorder in childhood (Pauls *et al.*, 1995), a considerable proportion of youth with OCD becomes subsyndromal (Stewart *et al.*, 2004).

We found neither sex differences in prevalence of CBCL-OCS (Hudziak *et al.*, 2006), nor in persistence. This is conform Stewart *et al.* (2004), who found sex to be a non significant predictor of persistence in OCD. If sex differences in prevalence of pediatric OCD are reported by others, boys outnumber girls, but this is mostly done in clinical samples (Geller *et al.*, 1998; Eichstedt & Arnold, 2001). This may imply that girls with OCS are less likely to be clinically diagnosed, although their symptoms are present and may persist into adolescence.

To what extent do early cases remit, do new cases emerge, and do others persist?

When we analyzed categorical stability, we found that very few children who meet cutpoint criteria at one age will meet it at the next. We found evidence of persistence to be rare and emergence of new cases and resilience being more common. These data are consistent with those of others who indicate that many children with OCD remit or recover (Stewart *et al.*, 2004). However, these data, taken together with the stability data provided by the quantitative analyses, also point to the weakness of using cutpoint approaches in phenotypes that appear to be quantitatively distributed. Children who initially scored at or above the cutpoint (5) and scored just below the cutpoint at a later age would categorically represent a remitted case and quantitatively be considered highly stable. For example, of all cases in table 2 who scored above the cutpoint at age 7 and scored lower than 5 at age 10, on average 50% had a CBCL-OCS score at age 10 of 3 or 4. When looking at interrater correlations across mothers and fathers using quantitative approaches, the degree of agreement is simply computed without concern for the cutpoint. Such approaches lead to increased power to test for agreement and disagreement.

To what extent do genetic or environmental influences account for stability of OC behaviour?

When using the more informative quantitative approach, we showed that, in boys, stability of OC behavior of ratings of both fathers and mothers is mainly due to additive genetic factors, especially for mother ratings. For girls, genetic and both shared and non-shared environmental influences are equally important in explaining stability of OC symptoms throughout childhood. For stability, the rater-specific phenotype was in general of less importance than the common phenotype.

In particular, fathers seem to add little extra information on stability of OC behavior. One might conclude that mothers are better aware of a long term view of OC behavior of their children.

Limitations

The results of this study should be interpreted in the context of several potential limitations: First, maternal and paternal data show high skewness and kurtosis. Derks *et al.* (2004) showed that skewness in the data lead to biases in parameter estimates, i.e. underestimation of the shared environmental estimates and overestimation of the non-shared environmental estimates. One approach to deal with this problem is using a liability threshold model (Lynch & Walsh, 1998). For the longitudinal design of the present study, however, a liability threshold model is practically not feasible.

Second, the genetic and environmental contributions presented in this report are for CBCL-OCS scores, not for clinical measures of DSM OCD. Although we have performed prior studies (Nelson *et al.*, 2001; Hudziak *et al.*, 2006), replicated by others (Geller *et al.*, 2006, Storch *et al.*, 2006), to demonstrate the validity, specificity, sensitivity and predictive power of the CBCL-OCS in relation to DSM-IV OCD, it remains possible that the CBCL-OCS may over identify cases in general population samples. However, as we have shown, the quantitative approach may be useful to identify children at risk for, but not yet expressing, DSM OCD.

Third, despite the fact that we used both maternal and paternal ratings, reliance on parental reports is still a limitation not easily corrected in children ages 7 to 12. Collection of Youth Self Report (YSR) (Achenbach, 1991) data in this sample when they become adolescents will be valuable in order to test the stability and change in OCS behavior across adolescents and young adults, where self reports become the mainstay of assessment. As a result, we currently aim to collect YSR data on these twins as they reach adolescence and young adulthood.

Fourth, one assumption underlying most twin designs is that the genetic and environmental latent factors show a continuous, normal distribution. Such distributions are implied if a large number of loci and environmental contributions, each with small individual effects, are present (Kendler, 2005). Van den Oord *et al.*, (2003) tested this assumption for self ratings of depression and found very little or no evidence of non-normality. This implies that there was no evidence that participants with high depressive score may be qualitatively distinct. Although it is likely that that this is also the case for OC symptoms/behavior, a psychiatric disease closely related to depression, we did not test whether the latent underlying factors are continuous.

Fifth, the findings of this analysis are predicated on the assumptions of the method used. These assumptions include absence of assortative mating and the equal environment assumption (EEA). The EEA states that environmental influences are shared to the same extent by MZ and DZ twins. Meas *et al.* (1998) found that significant but moderate primary assortment exists for psychiatric disorders. However, it was concluded that the bias in twin studies caused by the small amount of assortment is negligible. Jonnal *et al.* (2000) tested the EEA for OC symptoms and concluded that the EEA was not violated.

Implications

Our study has implications for clinical intervention. First our data, consistent with those of others, points to the fact that CBCL-OCS is a relatively unstable condition for which remission from 'clinical deviance' is a relatively common phenomenon. These data allow a clinician to have prognostic optimism when a parent asks about the future.

Second, and consistent with the literature on the power of behavioural approaches such as Exposure and Response Prevention (ERP) (Fisher & Wells, 2005) to positively affect OC behavior, our data point out the contribution of shared and unshared environment to phenotypic stability. Put simply, this finding argues strongly for changing the environment in children such that obsessions and compulsions will diminish (e.g. move kids out of the deviant group), for example by involving family members in the treatment of OCD (Renshaw *et al.* 2005).

Furthermore, this study has implications for measurement of behaviour problems. For cross-sectional heritability analyses, combining father and mother data adds extra information, suggesting that researchers studying children's behaviour problems in a cross-sectional design should try to collect data from different informants. For analyses of stability, mother ratings seem more informative than father ratings in our study. However, more longitudinal studies with multiple raters for different phenotypes are necessary to see if this is only the case for OC behavior. Within a clinical setting this could mean that interviewing both parents is important to get a good view about how the child is doing at the moment, while the information of the mother is important to get a long term view.

Lastly, this research has implications for molecular genetic research. Within the common phenotype of OC behaviour the same genes influence OC behaviour throughout at age 7, 10 and 12. It suggests that one may pool data from children of different ages together in linkage-analyses, obtaining an increase of power, and that no age-specific effects are to be expected in candidate gene studies.

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CHAPTER 8

Genetic and environmental contributions to self-report obsessive-compulsive symptoms in Dutch adolescents at age 12, 14 and 16

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Genetic and environmental contributions to self-report obsessive-compulsive symptoms in Dutch adolescents at age 12, 14 and 16

van Grootheest D. S., Bartels M., van Beijsterveldt C. E. M., Cath D. C., Beekman A. T., Hudziak J. J. & Boomsma, D. I.

ABSTRACT

Objective To determine the contributions of genetic and environmental influences to variation in self-report of ObsessiveCompulsive (OC) symptoms in a population-based twin sample of adolescent boys and girls.

Methods Self report ratings on the 8-item Obsessive-Compulsive Scale of the Youth Self Report (YSR-OCS) were collected in Dutch mono- and dizygotic twin pairs, who participated at age 12 years (N = 746 twin pairs), at 14 years (N = 963 pairs), or at 16 years (N = 1070 pairs). Structural equation modelling was used to decompose the variation in liability to OC symptoms into genetic and environmental components.

Results At age 12 no difference in prevalence was found for OC symptoms in boys and girls. At ages 14 and 16, the prevalence was higher in girls. At all ages, genetic factors contributed significantly to variation on OCS liability; 27% at the age of 12, 57% at the age of 14 and 54% at the age of 16. There were no sex differences in heritability. Only at age 12, environmental factors shared by children from the same family contributed significantly (16%) to individual differences in OC symptom scores.

Conclusions During adolescence, OC symptoms are influenced by genetic and non-shared environmental factors. Sex differences in prevalence, but not in heritability, emerge in adolescence. At age 12, shared environmental factors are of importance, but their influence disappears at later ages. This is in line with earlier research at age 12 which used parental ratings of OCS. Thus, between family factors play a significant role in explaining individual differences in OC symptoms at this age.

When considering the etiology of Obsessive-Compulsive Disorder (OCD) or Obsessive-Compulsive Symptoms (OCS), one could regard adolescence as a natural experiment during which a wide range of developmental and environmental changes occur over a short period of time. Therefore, this episode is of special interest when studying the dynamics between genes, development and environment. In OCD a bimodal distribution of age at onset has been found, with one peak occurring in preadolescent childhood and another peak in adulthood (Delorme *et al.*, 2005; Chabane *et al.*, 2005). Early age at onset of OCD is also associated with tic disorder (Swedo *et al.*, 1989; Rosario-Campos *et al.*, 2001) and the morbidity risk for OCD in family members of OCD subjects with early-onset of OCD is higher than in relatives of late-onset OCD probands (Pauls *et al.*, 1995; Nestadt *et al.*, 2000). Furthermore, adult studies report an equal representation of men and women for OCD, or a slight female preponderance, where in clinical studies early age at onset of OCD is associated with male preponderance (Geller *et al.*, 2001). These observations would suggest that adolescence could be a period in which genetic and environmental etiologic factors in OCD change over a relatively short period of time, offering a window of opportunity to study the genetics of OCD and OC symptoms. The aim of this study is to estimate the genetic and environmental contributions to OC symptoms in the adolescent period.

To disentangle genetic and environmental factors, twin or adoption studies are needed. No adoption studies of OCD have been published. Twin studies of OCD have evolved from case-studies with patients with OCD to large-scale studies of unselected subjects. In these studies, the entire distribution of OC Symptoms (van Grootheest *et al.*, 2005) is analyzed, assuming that OCS is continuous with OCD. Mathews *et al.* (2007) substantiated this assumption by finding evidence for a heritable unidimensional symptom factor underlying obsessionality. Additional evidence for this assumption comes from the observation that family members of OC patients have fewer OC symptoms that their family members with OCD, but more than controls (Pauls *et al.*, 1995).

In recent years several twin studies have been published examining Obsessive-Compulsive (OC) symptoms in children. Eley *et al.* (2003) examined 4564 four-year-old twin pairs in a British population-based twin study and included 4 items to assess OC symptoms. A heritability estimate of 65% was found. The remaining variance was accounted for by non-shared environmental influence. Hudziak *et al.* (2004) conducted a large twin study on OC behavior in children, assessed by the Child behavior Checklist Obsessive-Compulsive Scale (CBCL-OCS) (Nelson *et al.*, 2001; Hudziak *et al.*, 2006), in an American and a Dutch sample. OC behavior was assessed at ages 7, 10 and 12 years in the Dutch twins and at approximately 9 years in the American twins. Heritability in the Dutch sample was approximately 55% at age 7 and 10 years and dropped to 36% at age 12. The American sample showed a heritability of 55%. Small but significant shared environmental influences were seen at age 12 in the Dutch children. Significant sex differences in heritabilities were only seen in the USA data. Bolton *et al.* (2007) assessed 854 6-year old British twin pairs by maternal-informant diagnostic interviews using DSM-IV criteria. The effect of familial factors was estimated at 47% for sub-threshold OCD. The study lacked the statistical power to distinguish between shared environment and genetic factors to explain the familial aggregation. Lastly, follow-up research of the Hudziak *et al.* (2004) study investigated stability over time in twins aged 7, 10 and 12 years using a multi-rater design (van Grootheest *et al.*, 2007a). A moderate stability with phenotypic correlations of around .50 for boys and for girls was found. Stability of OC behavior was influenced by genetic factors, by environmental factors shared by children growing up in the same family, and by non-shared environmental factors. Shared environment was observed to be important especially at age 12.

In adults, Clifford *et al.* (1984) analyzed the 42-item version of the Leyton Obsessional Inventory (Cooper, 1970), obtained in 419 adult male and female twin pairs. The heritability of the obsessive symptoms was estimated at 47%. Jonnal *et al.* (2000) examined data from 527 pairs of female MZ and DZ twins from the Virginia Twin Registry, using 20 items of the Padua Inventory (Sanavio, 1988). The best model for these data suggested heritabilities of 33% and 26% for obsessiveness and compulsiveness respectively. Van Grootheest *et al.* (2007b) obtained the Young Adult Self Report Obsessive-Compulsive Subscale from 5893 mono- and dizygotic twins, and 1304 additional siblings and found a heritability of 39% in men and 50% in women.

As far as we know, no study has examined the genetic and environmental contributions to variation in OC symptoms during adolescence. In the current cross-sectional study, Dutch twins completed a self-report on OC behavior around their 12th, 14th or 16th birthday. We aim to determine the genetic architecture of OCS self report items in adolescence and to address the following questions:

1. What is the contribution of genetic and environmental influences on self-reported OC behavior in adolescence?
2. Are there sex differences in the contributions of genetic and environmental risk factors for OC symptoms in adolescence?

METHODS

Participants

The study was part of an ongoing study of emotional and problem behavior in young twins who are registered with the Netherlands Twin Register (NTR) (Boomsma *et al.*, 2006; Bartels *et al.*, 2007). We analyzed data from twin pairs who reported on their behavior with the Youth Self Report Obsessive Compulsive Scale when they were 12, 14 or 16 years old (Bartels *et al.*, 2007). A survey that contained the YSR-OCS was send by mail to the twins, after parents gave consent. Twins who did not return the forms within 2 months received a reminder. The overall family response rate was 56.1%.

Zygosity was determined by DNA or blood group polymorphisms in 52.4% of the same sex twin pairs. For the remaining same-sex twin pairs, zygosity was assessed by questionnaire items about physical similarity and frequency of confusion of the twins by family and strangers. Zygosity was correctly classified by questionnaire in 93% of the cases (Rietveld *et al.*, 2000).

Measures

The twins completed the 8 item Obsessive-Compulsive Scale of the Youth Self Report (YSR-OCS) (see table 1). The YRS-OCS was first developed and tested in young children using CBCL parental report (CBCL-OCS) (Nelson *et al.*, 2001; Hudziak *et al.*, 2006), and then tested on self-report data in the Young Adult Self Report, the YASR-OCS (van Grootheest *et al.*, 2007b). The YASR-OCS showed satisfactory psychometric properties with a sensitivity and specificity of 82% and 70% respectively in predicting OCD, when comparing an OCD group to a mixed psychiatric diagnoses group. Cronbach's alpha was .69. The YSR-OCS makes use of the same 8 items and showed a Cronbach's alpha of .67 within the current adolescent population (all ages taken together). Both the YSR-OCS and YASR-OCS have the same format as the CBCL-OCS (Nelson *et al.*, 2001), except that YSR and YASR items are worded in the first person. The CBCL-OCS showed high sensitivity and moderate specificity in predicting DSM-IV diagnosis of OCD in children and adolescents in several studies (Nelson *et al.*, 2001;

Table 1. YSR items used for the YSR-OCS

YSR item no	YSR item
9	I cannot get my mind off certain thoughts
31	I am afraid I might think or do something bad
32	I feel I have to be perfect
52	I feel too guilty
66	I repeat certain acts over and over
84	I do things other people think are strange
85	I have thoughts that other people would think are strange
112	I worry a lot

Table 2. Summary of studies examining psychometric properties of the CBCL-OCS that include the same 8 items as the YSR-OCS

Study	N of children/adolescents	Mean age (SD)	Sensitivity (compared to clinical controls)	Specificity (compared to clinical controls)	Crohnbach's alpha
Nelson *et al*., 2001	73 OCD patients and 73 clinical controls	12.3 (2.8) for boys 12.0 (2.6) for girls	75.3% - 84.9% (depending on percentile scores)	72.6% - 87.7% (depending on percentile scores)	.84
Hudziak *et al*., 2006	61 OCD patients and 64 clinical controls (in essence same population as used by Nelson *et al*.)	See Nelson *et al*.	92% (using a cut-off of 5)	67% (using a cut-off of 5)	See Nelson *et al*.
Geller *et al*., 2006	64 OCD patients and 64 clinical controls	11.2 (3.5)	78.1% - 92.2% (depending on percentile scores)	75% - 89.1% (depending on percentile scores)	.87

SD, Standard Deviation

Hudziak *et al*., 2006; Geller *et al*., 2006). We have summarized the psychometric results of the CBCL-OCS of these studies in table 2.

Analyses

MZ twins share all their genes, while DZ twins share on average half of their segregating genes. This different degree of genetic relatedness between monozygotic (MZ) and dizygotic (DZ) twins is used to estimate the genetic and environmental contributions to the variance of a trait. The total variance can be decomposed into additive genetic variance (A), shared environmental variance (C) and non-shared environmental variance (E). A is due to additive effects of different alleles, C is due to environmental influences shared by members of a family, and E is due to environmental influences not shared by members of a family. E also includes measurement error and is therefore always included in the models.

A first impression of the relative importance of each component is obtained by inspecting the twin correlations. MZ correlations twice as high as DZ correlations indicate additive genetic influences on twin resemblance. DZ correlations higher than half the MZ correlations designate shared environmental influences in addition to genetic influences. MZ correlations as high as DZ correlations indicate only shared environmental influences and no genetic sources of variance (Boomsma *et al.*, 2002). The proportion of phenotypic variance due to genetic influences is known as the heritability (h^2).

Structural equation modeling, as implemented in Mx (Neale *et al.*, 2003), was used for data analyses. Mx provides parameter estimates by maximizing the raw data likelihood. The goodness of fit of different models was evaluated by hierarchic likelihood ratio tests. Subtracting the two -2 loglikelihoods (-2LL) from each other yields a statistic that is asymptotically distributed as χ^2 with degrees of freedom (df) equal to the difference between the number of parameters in the two models. According to the principle of parsimony, models with fewer parameters (e.g. AE compared to ACE) were preferred if they did not give a significant deterioration in model fit. In addition, the Akaike Information Criterion (AIC) (Akaike, 1987), a goodness-of-fit index that considers the rule of parsimony, was calculated. More details of genetic model-fitting analyses are reviewed elsewhere (Neale and Cardon, 1992).

Because the data exhibited a pronounced right skew at all ages, we used a threshold model with three thresholds. By using a threshold model, genetic analyses are carried out on an underlying continuous distribution of liability to the disorder. The number of thresholds, defining categories (e.g. unaffected, mildly and severely affected (Derks *et al.*, 2004), are chosen in such a way that the number of individuals was roughly similar in each of the categories without the presence of empty cells (e.g., category not including any person).

We started with a saturated model, in which all thresholds and all twin correlations were estimated freely. Because a threshold model was used, polychoric correlations were obtained, which represent the resemblance between twins on the liability for OC symptoms. We tested whether thresholds were the same for first born and second born twins, for MZ and DZ twins to examine effects on prevalence of OC symptoms, and for boys and girls to examine sex differences in prevalence of OC symptoms. The saturated model provides a baseline model against which genetic models were compared. In the genetic models the significance of sex differences in the estimates for the influences of A, C and E were tested. The significance of the contributions of additive genetic influences and shared environmental influences was tested by assessing the deterioration in model fit after each component was constrained at zero in the full model.

Table 3. Number of complete twin pairs and twin correlations at age 12, 14 and 16

Zygosity	Age 12			Age 14			Age 16		
	Complete twin pairs	Incomplete twin pairs	Twin correlations	Complete twin pairs	Incomplete twin pairs	Twin correlations	Complete twin pairs	Incomplete twin pairs	Twin correlations
MZM	140	3	.50	134	5	.57	175	13	.45
DZM	138	2	.38	128	7	.17	130	16	.30
MZF	162	3	.45	222	9	.60	209	17	.58
DZF	124	6	.36	144	10	.30	189	13	.33
DOS	162	6	.21	272	32	.22	240	68	.22

MZM, monozygotic males; MZF, monozygotic females; DZM, dizygotic males; DZF, dizygotic females; DOS, opposite sex pair

RESULTS

In the saturated model, no effect of birth order or zygosity was detected at any age (all p-values > .05) on the thresholds. There was no sex effect on the thresholds at age 12 ($\chi^2(3) = 2.16.$, $p = .54$). However, at ages 14 and 16, the thresholds were significantly lower for girls ($\chi^2(3) = 43.94$, $p < .001$ and $\chi^2(3) = 42.57$, $p < .001$ respectively), indicating that girls score higher than boys on the YSR-OCS at the age of 14 and 16.

Polychoric twin correlations are presented in table 3 as a function of zygosity and age. At age 12 shared environmental factors seems to be of importance, because MZ correlations are less than twice the DZ correlations. Except for boys at age 16, with MZ correlations smaller than twice the DZ correlations, at age 14 and 16 MZ correlations are clearly about twice the DZ correlations, indicating the influence of genetic factors, but not of shared environment. The twin correlations in opposite-sex twin pairs were not attenuated compared with the correlations in same-sex dizygotic twin pairs (all p-values > .05) at three different ages. This means that there is no indication for sex-specific genes influencing variance in YSR-OCS scores.

Model-fitting results are given in table 4. Starting from the saturated threshold model, the full ACE threshold model with sex differences in variance components fits the data well at all ages (all p-values > .05). From the full model we constrained the estimates for additive genetic, shared environmental and non-shared environmental factors to be equal across the sexes. At all ages this model did not worsen the fit (all p-values > .05), meaning that the relative effects of these components were the same in boys and girls.

At age 12, the ACE model without sex differences gave a standardized estimate of .27 for genetic variance and .18 for shared environmental variance. We fitted both an AE and a CE model. Both models fit the data, although the AE model ($\chi^2(1) = 2.5$, $p = .12$) fit slightly better than de CE model ($\chi^2(1) = 3.5$, $p = .06$). A closer look at the AIC fit index showed that the ACE model without sex differences fit the data the best, suggesting that both genetic and shared influences play a role in individual differences in OC symptoms, regardless of sex.

At ages 14 and 16 the estimates of the shared environmental variance were zero. An AE model was the best fitting model for the data. Individual differenc-

Table 4. Model fitting results for YSR-OCS scores

Study Sample	Type of model	-2LL	χ^2	Δdf	p-value	AIC	Compared with model	Parameter estimates Boys a^2	Boys c^2	Boys e^2	Girls a^2	Girls c^2	Girls e^2
Age 12	1. Fully saturated	3939.5											
	2. ACE sex	3954.8	15.3	13	.29	1030.8	1	.23	.27	.51	.10	.33	.57
	3. ACE no sex	**3958.0**	**3.2**	**2**	**.20**	**1030.0**	**2**	**.27**	**.18**	**.54**	**.27**	**.18**	**.54**
	4. AE no sex	3960.5	2.5	1	.12	1030.5	3	.49	.00	.51	.49	.00	.51
	5. CE no sex	3961.6	3.6	1	.06	1031.6	3	.00	.38	.62	.00	.38	.62
Age 14	1. Fully saturated	4923.4											
	2. ACE sex	4935.7	12.3	13	.50	1229.7	1	.54	.01	.46	.50	.09	.41
	3. ACE no sex	4936.9	1.2	2	.27	1226.9	2	.57	.00	.43	.57	.00	.43
	4. AE no sex	**4936.9**	**0.0**	**1**	**.99**	**1224.9**	**3**	**.57**	**.00**	**.43**	**.57**	**.00**	**.43**
Age 16	1. Fully saturated	5246.2											
	2. ACE sex	5260.7	14.5	13	.34	1254.7	1	.45	.05	.50	.55	.04	.42
	3. ACE no sex	5262.7	2.0	2	.16	1252.7	2	.54	.00	.46	.54	.00	.46
	4. AE no sex	**5262.7**	**0.0**	**1**	**.99**	**1250.7**	**3**	**.54**	**.00**	**.46**	**.54**	**.00**	**.46**

LL, log-likelihood; χ^2, chi-square; df, degrees of freedom; AIC, Akaike Information Criterion; A, additive genetic effects; C, shared environmental effects; E, non-shared or individual-specific effects. Boldface type represents the best-fitting model for that sample. a^2, c^2, e^2 show the proportion of variance of A, C and E respectively and is calculated by squaring the parameters

es in OC symptoms were explained by additive genetic influences (57% and 54% at age 14 and 16 respectively) and non-shared environmental effects (43% and 46% at age 14 and 16 respectively). Next we tested if genetic and non-shared environmental influences were of the same magnitude for adolescents at 14 and 16 years of age. At both ages genetic influences accounted for 55% of the variation in OC symptoms and non-shared environmental influences were estimated to account for 45% ($\chi^2(1) = .253$, $p = .61$).

DISCUSSION

To our knowledge, this is the first twin study of OCS in adolescents, revealing that individual differences in OCS are heritable throughout puberty, with shared environmental influences only playing a role at the beginning of adolescence. No sex differences in heritability estimations were found, and individual differences in OCS are influenced by the same additive genetic factors in boys and girls. Female adolescents scored higher on OCS than males at the age of 14 and 16, but not at the age of 12.

The finding of equal prevalence of OC symptoms in boys and girls at age 12 is in line with the study of Hudziak *et al.* (2004), who found no sex differences in scores at age 7, 10 and 12. The prevalence of OCS in boys and girls within community samples seems to be more similar than in clinical samples with OCD, where boys outnumber girls. Interestingly, at the age of 14 and 16 girls showed a higher OCS prevalence than boys. This is in line with a recent study using the YASR-OCS in adults, which found significantly higher prevalence for women and also with clinical and epidemiological findings of a slight preponderance in the prevalence of OC symptoms in women (van Grootheest *et al.*, 2007b). These results strongly suggest that sex differences in prevalence develop in early puberty and that these sex differences persist until adulthood.

The finding of shared environmental influences of 18% in this study at age 12 is remarkably similar to that of 16% found in the study of Hudziak *et al.* (2004), who used essentially the same sample as the current paper. Note that the study of Hudziak *et al.* (2004) presented mother ratings, whereas the current paper used self reports. Van Grootheest *et al.* (2007a) also found shared environmental influences to be important (approximately 30%) at age 12 using a design with both maternal and paternal ratings of OC symptoms. This means that the same results, i.e. no sex differences in prevalence and significant shared environmental influences, were found in a variety of studies using different ratings and raters, underscoring the relevance of these shared influences at age 12. Recently, we also found shared environmental influences at age 12 to be important for loneliness (Bartels *et al.*, 2008) and depression/anxiety (Boomsma *et al.*, 2008). This could mean that shared environmental influences are not specific for OC symptoms, but indicate an age-dependent family environment factor to exacerbate internalizing psychopathology in general at that age. The question remains as to which factors cause the emergence of shared environmental influences at this age. Although somewhat speculative, the age of 12 is the key-age for the transition from primary to secondary school in the Netherlands, a well-known stressful event (Sirch, 2003). When leaving the old school to enter the new, children leave their old peer group to build up a new one, and therefore rely more on family life than before. Considering the demands in this transitional period, families may differ in dealing with these stressful events. This conclusion also has clinical consequences. Given that cognitive behavioral therapy could clearly be seen as a potential environmental mediator of OC symptoms, involving family members in behavioral treatment of OC symptoms may be best aimed at the very young when shared environment is in play (Renshaw *et al.*, 2005).

A closer look at the heritability estimates over time reveals that OCS is remarkably stable, with heritability estimates of approximately 55% at younger ages (Hudziak *et al.*, 2004), with a drop at age 12, where part of the variance was accounted for by shared environmental influences, continuing to 55% at ages 14 and 16, and 45% in adulthood (van Grootheest *et al.*, 2007b). This drop in heritability between children/adolescents and adults may reflect the bimodal distribution found in the clinical OCD literature (Delorme *et al.*, 2005; Chabane *et al.*, 2005), which found early onset OCD to be associated with a higher genetic load in comparison with late onset OCD.

By demonstrating that genetic factors are influencing OC symptoms also in adolescence, gene finders are given a strong signal to pursue. However, a relatively stable heritability does not automatically imply that the same genes are involved at different ages. Only longitudinal data can elucidate whether the genes associated within childhood (van Grootheest *et al.*, 2007a) also persist in adolescence and even in adulthood. As the NTR is growing and the twins are getting older, future studies will focus on longitudinal analyses of OC symptoms from childhood to adolescence to adulthood.

The results of this study should be interpreted in the context of several potential limitations. First, the genetic and environmental contributions presented in this report reflect YSR-OCS scores, not clinical measures of DSM-IV OCD. Because of the relatively low prevalence of OCD, twin studies rely on dimensional measures with the underlying assumption that OCD reflects the end of a normal distribution, while OC symptoms represent a milder form of the latter (Jonnal *et al.*, 2000; van den Oord *et al.*, 2003; Kendler, 2005). Since the current twin analyses are based on a liability threshold model, it should make no difference if the studied variable is dimensional, as long as it reflects the same underlying liability as the categorical diagnosis (Reichborn-Kjennerud *et al.*, 2007).

Second, the use of twin models requires several assumptions, including the absence of assortative mating, the equal environment assumption (EEA), and the absence of gene-environment interaction and correlation. Van Grootheest *et al.* (2008b) found that small, but significant assortative mating existed for OC symptoms but concluded that the bias in twin studies caused by the small amount of assortment is negligible. Jonnal *et al.* (2000) tested the EEA for OC symptoms and concluded that the EEA was not violated. Gene-environment interaction could affect twin similarity in either direction depending on whether both twins are exposed to the specific environmental factor in question; to our knowledge, gene-environment interaction and/or correlation have yet to be demonstrated for the phenotype studied here.

Thirdly, the 8-item YSR-OCS is not suitable to examine OC symptom dimensions. More and more evidence is coming out that OCD or OCS appears to encompass at least four consistent and temporally stable symptom dimensions (Mataix-Cols et *al.*, 2005). By considering these OC symptom dimensions as quantitative components of a more complex OC phenotype, a dimensional approach could provide a more powerful approach for the detection of genes or environmental risk factors that contribute to OC behavior (Miguel *et al.*, 2005). We recently found evidence for specific genetic and environmental factors underlying the Contamination dimension (van Grootheest *et al.*, 2008a) underscoring the potential value of OC symptoms dimensions in this field of research (Leckman *et al.*, 2007).

In sum, the present study suggests that heritability estimates of OC symptoms in adolescence are similar (55%) to the heritability estimates in children, with a drop around the age of 12. At 12 years a clear contribution of shared environment was found to the variation of OC symptoms. Sex differences in scores on OC symptoms were found, with girls scoring higher than girls on OCS at the age of 14 and 16, but not at age 12. The current study underscores the importance of conducting more research to OCS in the adolescent period.

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CHAPTER 9

Genetic factors are the most important cause for stability of obsessive-compulsive symptoms: a report from the Netherlands Twin Register

van Grootheest, D. S., Hottenga, J. J., Beekman, A. T., Cath, D. C. & Boomsma, D. I.: Genetic factors are the most important cause for stability of obsessive-compulsive symptoms: a report from the Netherlands Twin Register *(submitted).*

Genetic factors are the most important cause for stability of obsessive-compulsive symptoms: a report from the Netherlands Twin Register

van Grootheest, D .S., Hottenga, J. J., Beekman, A. T., Cath, D. C. & Boomsma, D. I.

ABSTRACT

Background The contribution of genetic and environmental factors to the stability of OC symptoms has not been examined before in a population based sample of adults.

Methods We obtained the Young Adult Self Report Obsessive-Compulsive Subscale (YASR-OCS) in a group of mono- and dizygotic twins from the population-based Netherlands Twin Register in 1991, 1995 and 1997 and the Padua Inventory Revised Abbreviated in 2002. Stability of obsessive-compulsive (OC) symptoms was examined and analyzed as a function of genetic and environmental components.

Results Results Heritability of OC behavior was around 40% at each time-point, independent of the instrument used. OC behavior was moderately stable with correlations between .39 and .61 for subsequent time-points. However, genetic correlations across time were much higher, varying between .61 and .90 for subsequent time-points, indicating that the stability of OC symptoms is mainly due to the same genetic factors.

Conclusions Stability of OC behavior was predominantly due to stable genetic factors.

To date, research on persistence of Obsessive-Compulsive Disease (OCD) and/or Obsessive-Compulsive (OC) symptoms has concentrated on subjects who are patients. Several older studies on the course of OCD have suggested it to be chronic and lifelong with waxing and waning symptom severity (Goodwin *et al.*, 1969). More recent studies on the course of OCD showed varied results; some studies concluded that OCD is a chronic illness with low rates of remission (Rasmussen & Tsuang, 1986; Eisen *et al.*, 1999; Alonso *et al.*, 2001), whereas other studies showed less pessimistic findings with conclusions that about 50% of patients remit (Orloff *et al.*, 1994; Skoog & Skoog, 1999; Steketee *et al.*, 1999; Reddy *et al.*, 2005; Angst *et al.*, 2004). Reddy *et al. (2005)* concluded that poor outcome in previous studies may have been due to the inclusion of severely and chronically ill patients. Only one study examined OCD and OC symptoms in a community cohort. The Zurich community cohort study (Angst *et al.*, 2004) followed a group of adolescents for almost 20 years and concluded that, although the course of OC symptoms was described as chronic by 60% of the subjects, symptoms ameliorated in most subjects. Within paediatric obsessive-compulsive disorder, Stewart *et al.* (2004) conducted a meta-analysis of the long-term outcome and found pooled mean persistence rates of 41% for full OCD and 60% for full or subthreshold OCD.

These data provide a longitudinal perspective on OCD and OC symptoms in adults, but no investigations have been conducted to date into its underlying etiology. To our knowledge, only one study has examined stability of OC symptoms including the genetic architecture of stability, but this study comprised a young twin sample aged 7 to 12 (van Grootheest *et al.*, 2007a). Van Grootheest *et al.* (2007a) found that OC behavior is moderately stable in childhood with correlations of .5 across age. Stability of OC behavior was influenced for roughly 40% by genetic factors and the rest of the variation was explained by shared (e.g., family factors) and non-shared environmental factors (e.g., individual experiences).

The purpose of the present study is to explore the stability of OC symptoms and determine the genetic and environmental contributions to stability of OC symptoms using longitudinal OC symptom data from a large sample of adult twins. OC symptoms were measured in 1991, 1995, 1997 and 2002. We aimed to address the following questions:

1. What is the stability of OC behavior in adults over time?
2. To what extent do genetic or environmental influences account for stability of OC behavior?

METHODS AND MATERIALS

Subjects and Procedure

This study is part of a longitudinal survey study in twin families registered with the Netherlands Twin Register (Boomsma *et al.*, 2002b; Boomsma *et al.*, 2006). Since 1991, every two to three years twins and their families have received a survey by mail containing questionnaires about health, personality and lifestyle. For the present study, we included OC data of adolescent and adult twins from wave 1991, 1995, 1997 and 2002. Table 1 gives an overview of the complete and incomplete twin pairs included in de study, presented by time-point and zygosity. The total sample consists of twins from 4198 different families. Four hundred and forty one twin pairs participated at four time-points; 734 twin pairs participated three times; 1102 twin pairs participated twice, and 1921 twin pairs participated once. If a twin did not respond at a particular time point they were approached for the next mailing. In 1991 and 1995, adolescent and young adult twins were recruited through City Council Registrations. From 1997 onwards an additional effort was made to recruit older twins for the study. This effect is reflected by the mean ages per time-point, which were 17.8 (SD 2.3) in 1991, 19.8 (SD 3.2) in 1995, 25.5 (SD 9.8) in 1997 and 33.0 (SD 13.5) in 2002.

Table 1. Number of complete and incomplete twin pairs with OC data at time-points 1991, 1995, 1997, and 2002

	1991		1995		1997		2002	
zygosity	Complete twin pairs	Incomplete twin pairs	Complete twin pairs	Incomplete twin pairs	Complete twin pairs	Incomplete twin pairs	Complete twin pairs	Incomplete twin pairs
MZM	273	0	272	10	216	76	236	181
DZM	231	11	223	6	147	64	99	151
MZF	380	3	422	15	407	120	631	342
DZF	280	3	258	16	244	107	293	251
DOS	473	6	453	36	318	166	290	383

MZM, monozygotic males; MZF, monozygotic females; DZM, dizygotic males; DZF, dizygotic females; DOS, opposite sex pair

Zygosity of the twins was determined using items about physical similarity and the frequency of confusion of the twins by family and strangers. Of 869 same sex twin pairs, zygosity information was available from DNA polymorphisms. The agreement between zygosity information from the questionnaire and DNA data was 97% (Willemsen *et al.*, 2005).

Measures

At wave 1991, 1995 and 1997, OC symptoms were measured with the Young Adult Self Report Obsessive-Compulsive Scale (YASR-OCS) (van Grootheest *et al.*, 2007b). At wave 2002, OC symptoms were measured with the Padua Inventory abbreviated (PADUA ABBR) (Cath *et al.*, 2008).

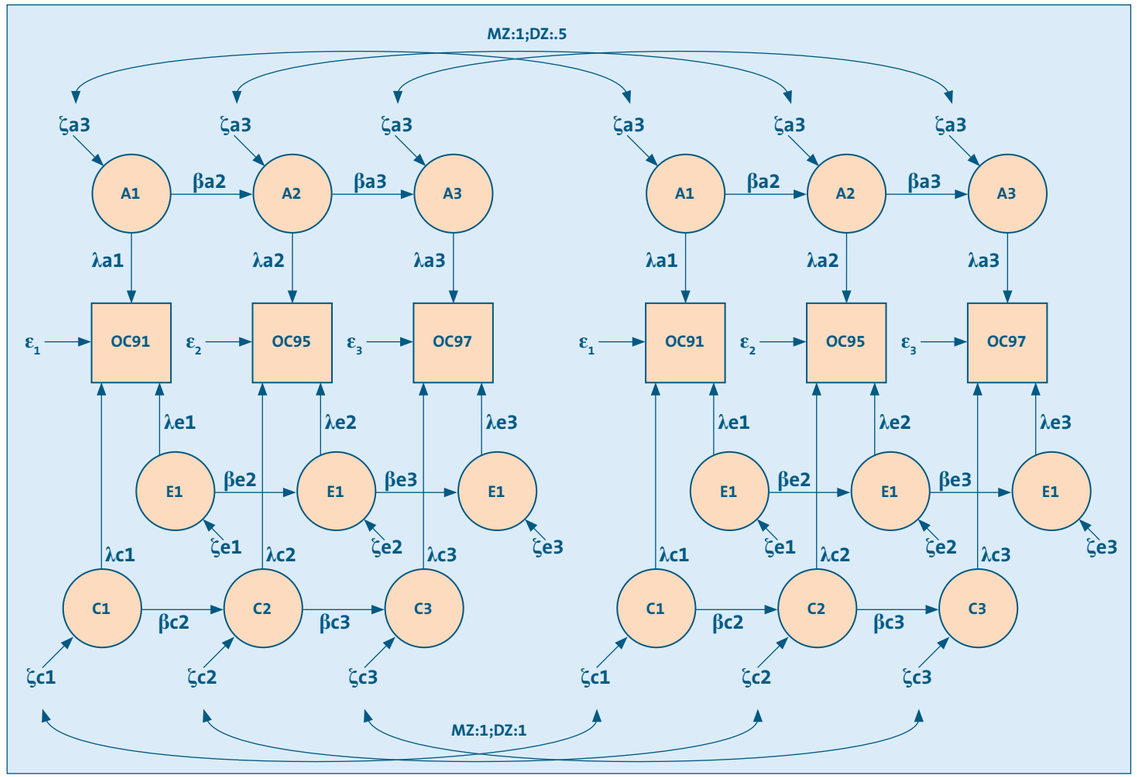
The Young Adult Self Report (YASR) encompasses a standardized self-report questionnaire for adolescents and adults (Achenbach, 1997). It is derived from the Child Behavior Checklist, a parent-derived rating instrument for children between 4-18-years old (Achenbach, 1991). The YASR roughly has the same format as the CBCL, except that items pertaining to childhood problems are replaced by items pertaining to adults' functioning. The YASR comprises 110 problem items, covering emotional and behavioral problems during the previous 6 months. The participants respond on a 3 point scale with the code of 0 for not true, 1 for somewhat or sometimes true and 2 for very true of often true. A good reliability and validity of the YASR has been reported by Achenbach (Achenbach, 1997) and was supported for the Dutch version (Wiznitzer *et al.*, 1992; Verhulst *et al.*, 1996). The YASR-OCS contains 8 OC items from the YASR, and is similar to the CBCL-OCS (Nelson *et al.*, 2001; Geller *et al.*, 2006; Hudziak *et al.*, 2006), except that items are worded in the first person. A numerical value for the YASR-OCS is obtained by adding the scores on the relevant 8 items (0, 1 or 2 per item), thus limiting the scale to a range between 0 and 16. Using a cut-off of 7 on the YASR-OCS, 82.4% of all DSM-determined OCD cases were identified in a clinical sample of children with reasonable specificity (69.7%). Cronbachs' α of the scale was 0.69.

The Padua Inventory abbreviated (PI-R ABBR) (Cath *et al.*, 2008) has been derived from the Padua Inventory-Revised (PI-R), the latter being a widely used self report inventory on obsessive-compulsive symptoms (Sanavio E, 1988; Oppen van, 1992). The PI-R is a 41 item self-report instrument that measures OC symptoms on a 0-4 scale, and contains 5 subscales, i.e. washing, checking, rumination, precision and impulses (Oppen van *et al.*, 1995). It has been validated in the Netherlands, shows good psychometric qualities, and moderately correlates (Denys *et al.*, 2004) with the Y-BOCS symptom checklist, a clinician-derived checklist on OC symptoms (Goodman *et al.*, 1989). For the aim of this epidemiological twin study, the PI-R was reduced to 12 items. Item choice was based on 2 items of each subscale with highest factor loadings in a previous validation study (Oppen van *et al.*, 1995), and with one additional item for each of the more equivocal obsession subscales rumination and impulses. Cronbachs' α of the scale was 0.73, which is an indication of good internal consistency. Sensitivity and specificity of the PI ABBR to detect DSM IV OCD was .74 and .72 respectively, when compared to clinical controls (Cath *et al.*, 2008).

Analyses

Analyses were conducted using structural equation modelling, with the statistical software package Mx (Neale *et al.*, 2006). In longitudinal studies such as the

Figure 1. Full ACE simplex model for the observed variable OC symptoms



Full ACE simplex model for the observed variable OC symptoms (squares), which is measured across four time-points (OC91, OC95, OC97 and OC02). Because of space limits we show only the first 3 time-points. The loadings of the observed variables on the latent factors (λ) are set to unity. The variances of the innovations terms (ζ) are estimated. A measurement error term also influences the variance of each observed variable and is equated across twins and in our model for the first three measurements. The weights are solely responsible for the covariation among variables. Correlations between co-twins for additive genetic factors (A) are fixed to one for MZ twin pairs and .5 for DZ twin pairs. Correlations for shared environmental factor are one for both MZ and DZ twin pairs. Non-shared environmental factors are uncorrelated between co-twins.

current one, not all subjects have taken part in the study at all occasions. To be able to use all data, full-information maximum likelihood estimation with raw data was used. For each family, twice the negative log-likelihood (-2LL) of the data is calculated, and parameters are estimated so that the overall likelihood of the raw data is maximized. The fit of the genetic models and submodels were compared with likelihood-ratio tests, by subtracting -2LL for a restricted nested model from -2LL of a less restricted model. The resulting test statistics has a χ^2 distribution with degrees of freedom (df) equal to the difference of the df between the models. The saturated model, a model in which the covariance matrix and the mean structures are computed without any restriction, was used as a reference to test for the homogeneity of means and variances, constraining them to be equal across zygosity and sex. The type-I error rate of all statistical tests was set at .01 to accommodate multiple testing.

GENETIC MODELLING

Twins may resemble each other because they share their pre-and postnatal environment, often referred to as shared or common environment (C). In addition, DZ twins may resemble each other because they share 50% of their additive genetic variance (A). MZ twins share all the additive genetic variance, because they have identical genotypes. Thus, additive genetic factors are correlated 1 across MZ twin pairs and .5 across DZ pairs. Shared environmental factors are correlated 1 for MZ and DZ twins. Non-shared factors (E) refer to individual experiences and are uncorrelated for MZ and DZ twins by definition (Boomsma *et al.*, 2002a).

To analyze the longitudinal data for twins, a simplex model or transmission model was employed, which is a developmental model that may explain the pattern of correlations across time-points. The simplex model is most suitable for longitudinal series in which there is occasion-to-occasion transmission and when

Table 2. Age of twin and means and variances of YASR-OCS (1991, 1995 and 1997) and PI-R ABBR (2002)

	Age (SD)				Mean				Variance			
	1991	1995	1997	2002	1991	1995	1997	2002	1991	1995	1997	2002
MZM	17.6 (2.3)	19.7 (3.1)	25.4 (9.9)	32.8 (11.9)	2.2	1.8	1.8	7.9	4.2	3.9	3.7	32.8
DZM	17.6 (2.2)	19.8 (3.1)	25.2 (9.6)	33.1 (11.5)	2.4	2.2	2.1	7.6	4.9	4.6	4.8	30.4
MZF	17.6 (2.1)	19.6 (3.1)	26.4 (10.5)	33.5 (11.7)	2.7	2.7	2.6	8.2	5.6	5.4	5.5	33.1
DZF	17.8 (2.4)	20.0 (3.2)	26.0 (10.0)	32.9 (11.0)	3.0	2.6	2.6	7.8	6.5	6.1	5.6	27.8
DOS-M	17.8 (2.2)	20.0 (3.2)	24.3 (8.9)	31.2 (9.9)	2.5	2.3	2.0	8.3	5.3	5.0	4.1	28.1
DOS-F					2.9	2.6	2.5	8.2	5.5	5.2	5.3	30.5

MZM, monozygotic males; MZF, monozygotic females; DZM, dizygotic males; DZF, dizygotic females; DOS-M, male half of a complete dizygotic opposite sex pair; DOS-F, female half of complete dizygotic opposite sex pair; SD, standard deviation

correlations decrease with increasing distances between time-points (Boomsma & Molenaar, 1987). Figure 1 represents the simplex model, because of space limits only for 3 time-points. It includes causal pathways or transmission effects (β in figure 1) between genetic (A) or environmental (C or E) latent factors that influence the trait at different occasions. As a result, genetic or environmental factors (A, C or E) at a particular time-point are influenced by factors preceding that time-point. Furthermore, the model includes innovations (ζ in figure 1) (Neale & Cardon, 1992). The innovation is that part of the latent factor that is not caused by a latent factor at a preceding occasion. At the first occasion the first latent factor cannot be explained by factors associated with an earlier point in time, and therefore this factor itself is regarded as an innovation (van Beijsterveldt *et al.*, 2003). In a genetic study, the genetic innovations represent the expression of a new set of genes.

The simplex model is also able to distinguish the non-shared environmental variance in measurement error (ε in figure 1) and "real" non-shared environmental innovations (**ζe** in figure 1). There is an important conceptual distinction between innovations of latent variables and measurement errors of observed variables. The innovations are the part of the latent variable at time i that is not caused by the latent variable at time i-1, but are part of every subsequent observed variable, i + 1, i + 2 etc. In contrast, the random errors of measurement are terms that do not influence subsequent observed variables (Cornes *et al.*, 2007).

In figure 1, λ represents the loadings of the observed phenotype on the latent factors. In the current study, these loadings were set to unity, so that the scaling of the latent factors is identical to the scaling of the phenotype. The variance of all measurement error terms was constrained to be equal in order for the model to be identified. Because at occasion 4, a different questionnaire was used with larger variance than in the first three occasions, the variance of measurement errors could not constrained to be equal. We therefore constrained the first 3 measurement error terms to be equal and fixed measurement error term at occasion 4 at zero. This means that for time-point 4, the measurement error is included in the innovation at time-point 4.

To test the fit of the simplex model, a Cholesky model was used as reference model (Neale & Cardon, 1992). The Cholesky decomposition is descriptive and not driven by a specific developmental hypothesis. The model is a saturated unconstrained model and it decomposes a covariance matrix into genetic and non-genetic covariance matrices and thus is a first approach to obtain genetic and environmental correlations across time in longitudinal datasets.

RESULTS

Sample characteristic and descriptive statistics

Table 2 summarizes the means and variances for the YASR-OCS and the PI-R ABBR. No significant differences in means and variances over zygosity were seen for men and women at all 4 time-points, except at time-point 1995 ($\chi^2(8.74) = 2$, $p < .01$). At that time-point DZ men scored higher on the YASR-OCS than MZ men. Significant sex-differences were seen at time-point 1991, 1995 and 1997 with women scoring higher on the YASR-OCS than men (all $p < .01$). At time-point 2002, women seem to score higher on the PI-R ABBR, but this was non-significant ($\chi^2(2.78) = 1$, $p = .10$). The same pattern is also seen for the variances; significant variance differences between men and women for the first three time-points (all $p < .01$) and a non-significant difference for the last time-point ($\chi^2(0.49) = 1$, $p = .48$).

Table 3 shows the within-person phenotypic correlations over time for men and women. OC behavior was moderately stable with correlations between .39 and .61 for subsequent time-points for men and women, with somewhat lower correlations between .16 and .42 for non-subsequent time-points with lower correlations

Table 3. Within person correlations over time of YASR-OCS (1991, 1995 and 1997) and PI-R ABBR (2002)

	1991	1995	1997	2002
1991	1	.48	.42	.25
1995	.41	1	.61	.32
1997	.35	.52	1	.40
2002	.16	.28	.39	1

Correlations for men and women are reported below and above diagonal respectively

Table 4. Twin correlations for YASR-OCS (1991, 1995 and 1997) and PI-R ABBR (2002) and cross twin-cross time correlations

	Cross Twin-Within Time Correlations				Cross Twin-Cross Time Correlations					
zygosity	**1991**	**1995**	**1997**	**2002**	**91-95**	**91-97**	**91-02**	**95-97**	**95-02**	**97-02**
MZM	.41	.39	.46	.37	.30	.38	.23	.38	.22	.28
DZM	.10	.24	.11	.35	.05	.01	-.02	.31	-.05	.06
MZF	.35	.53	.47	.44	.33	.34	.18	.51	.25	.26
DZF	.25	.25	.32	.21	.30	.19	.18	.19	.08	.12
DOS	.17	.18	.19	.19	.18	.15	.17	.20	.16	.14

MZM, monozygotic males; MZF, monozygotic females; DZM, dizygotic males; DZF, dizygotic females; DOS, dizygotic opposite sex

for longer time intervals. The correlations between the YASR-OCS at time-point 1997 and PI-R ABBR at time-point 2002 were essentially the same (.39 for men and .40 for women) as between the YASR-OCS at time-point 1991 and 1995 (.41 for men and .48 for women), both intervals covering about the same time interval.

The summary of twin correlations at each time-point and of the cross-twin-cross-time-point correlations is shown in table 4. The twin correlations within time-points show that MZ correlations are generally higher than DZ correlations in both men and women. This suggests that both genes and non-shared environmental influence explain individual differences in OC symptoms. Only at time-point 2002 and only in men, the DZ correlation is close to the MZ correlation, suggesting the influence of shared environment at that time-point. Cross-twin-cross-time-point correlations represent the correlations between the OC symptom score at one time-point (e.g., 1991) in one twin, with the OC symptom scores of another time-point for another twin. Correlations between first-born and second-born twins are constrained to be equal to correlations between second-born and first-born twins. As can be seen, for almost all cross-correlations the MZ correlations are higher than DZ correlations, indicating the influence of genes on covariance of OC symptoms across time.

Genetic analyses

Table 5 displays the series of model fitting analyses conducted to test which model best described the data. The simplex model fitted very well against the Cholesky model. As expected from the twin correlations, the estimates for shared environmental factors were low (data not shown), therefore an AE simplex model was fitted. This model provided an adequate fit (model 3 in Table 5). To test whether the parameter estimates differed between men and women, the parameters of the final model were constrained to be equal across sex, and the fit of the model was compared with the model without sex differences. The fit of the model without sex differences deteriorated significantly (model 4 in Table 5), because of variance differences between men and women. This means that the AE simplex model with sex differences is the best fitting model (bold in Table 5).

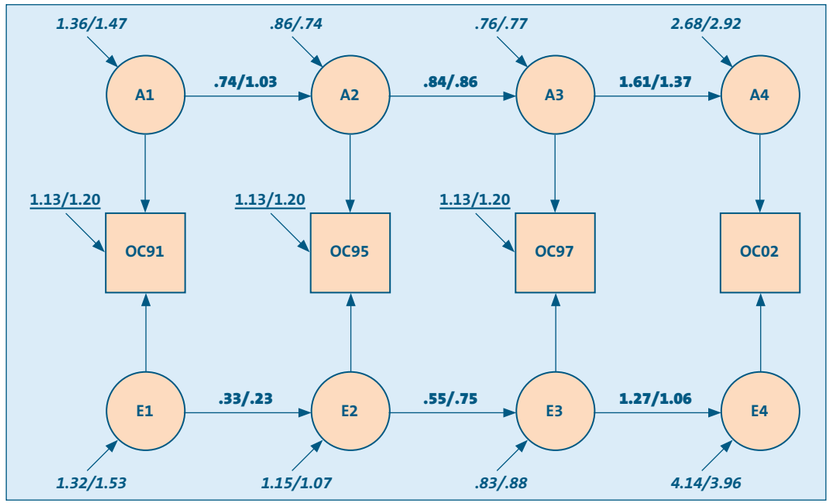
Table 5. Model fitting results; Cholesky and Simplex models for YASR-OCS (1991, 1995 and 1997) and PI-R ABBR (2002)

Type of model[a]	-2LL	χ^2	Δdf	P value	Compared with model
1. Cholesky ACE	69400.1				
2. Simplex ACE	69407.0	6.9	16	.98	1
3. AE	**69419.8**	**12.8**	**14**	**.54**	**2**
4. AE, no sex differences	69473.8	54.0	15	.00	3

[a] A=additive genetic effects; C=shared environmental effects; E= nonshared or individual-specific effects. -2LL, log-likelihood; χ^2, chi-square; Δdf, difference in degrees of freedom

Figure 2 shows the unstandardized estimates of the final model. These estimates can be used to compute the relative contributions of A and E to the time-point specific total variances and stability coefficients. The genetic contribution to OC symptoms at each time-point consisted of genetic influences novel to that time-point (= innovation effect, italics in figure 2), plus the genetic effects that were already operating at a previous time-point (= transmission effect, bold in figure 2). The standardized innovation effect is achieved by dividing the squared innovation coefficient by the total variance. For example, the innovation effect at time-point 97 for boys is $(.76^2)/4.21 = 14\%$. The percentage of the genetic variance at time-point 97 that is transmitted from time-point 95 can be obtained by dividing the product of the squared transmission coefficient ($.84^2$) and the genetic variance of the previous time-point (1.36^2 x $.74^2$ + $.86^2$ = 1.75) by the total variance: ($.84^2$) x 1.75/4.21 = 29%. This means that 43% (14% + 29%) of the total variation of individual differences in OC symptoms is caused by genetic factors. An overview of the relative contribution of A and E for each time-point is given on the diagonal of the first part of table 6 for men (top part) and women (lower part). At each age the contribution of genetic factors was substantial and remained quite stable across time-points and appears independent from the questionnaire used. Averaged over time-points, 40% (for men) and 45% (for women) of the variance was explained by genetic factors. The contribution of time-point specific genetic factors differed across time-points and across sex. At time-point 95 and time-point 97, about 20% of the total variance consisted of new genetic variance for girls, with a percentage of 40 for boys. At time-point 2002, using the PI-R ABBR instead

Figure 2. Unstandardized estimates of the simplex model for OC symptoms at four time-points for men (left) and women (right)



The squares represent the observed variance for each time-point (OC91, OC95, OC97 an OC02). The circles represent the latent factors. A=genetic influences, E=nonshared influences. We distinguished innovation effects (italics), transmission effects (bold) and measurement error (underscore).

of the YASR-OCS at earlier time-points, about 60% of the genetic variation is new genetic variation for both women and men.

For non-shared environmental variance the transmission for men and women was low and varied between 2% and 13%. Most non-shared environmental variance consisted of time-point specific variance. Measurement error explains roughly 25% and 28% of the total variance for women and men respectively at the first 3 time-points. For time-point 4 the measurement error was included in the total non-shared environmental variance.

The off-diagonal estimated in table 6 summarizes the results regarding the decompositions of the phenotype stability across time. The results show that about 70% and 80% of the stability in adulthood is a result of additive genetic effects for respectively men and women. The contributions of non-shared environmental factors to the stability were small.

The correlations in table 7 indicate the degree of overlap between genetic and environmental influences at one age and influences at subsequent time-points. The additive genetic correlations are estimated between .63 and .82 for men between the first three time-points with correlations of .39 and .63 between the first three time-points and the last time-point. For women, the correlations varied between .80 and .90 between the first three time-points, and .49 and .61 for the last time-point. These high genetic correlations suggest that there is a high overlap between time-points of the same genetic influence in adulthood using the same scale, but somewhat lower between two different measures. This last finding was already reflected in the high genetic innovation at the last time-point in figure 2.

Table 6. Relative contributions of additive genetic and non-shared environmental components to the total variances (diagonal) and covariances (off-diagonal) for YASR-OCS (1991, 1995 and 1997) and PI-R ABBR (2002) in men and women

	Additive genetic architecture (A)				Non-shared environment architecture (E)			
Men	**1991**	**1995**	**1997**	**2002**	**1991**	**1995**	**1997**	**2002**
1991	.38				.62 (*.36* + 26)			
1995	.70	.39 (**.22** + *.17*)			.30	.61 (**.04** + *.29* + 28)		
1997	.78	.64	.43 (**.29** + *.14*)		.22	.36	.57 (**.10** + *.17* + 30)	
2002	.82	.69	.67	.38 (**.15** + *.23*)	.18	.31	.33	.62 (**.06** + *.56*)
Women								
1991	.36				.64 (*.40* + 24)			
1995	.81	.51 (**.41** + *.10*)			.19	.49 (**.02** + *.21* + 26)		
1997	.83	.72	.47 (**.37** + *.10*)		.17	.28	.53 (**.13** + *.14* + 26)	
2002	.86	.77	.70	.44 (**.16** + *.28*)	.14	.23	.30	.56 (**.05** + *.51*)

Note: On the diagonals, the genetic influences are partitioned into transmission effects (bold) and innovation effects (italics). The non-shared influences are partitioned into transmission effects (bold), innovation effects (italics) and measurement error (underscore)

Table 7. Correlations calculated for additive genetic and non-shared environmental sources of variance between the different time-points. Correlations for men and women are reported below and above diagonal, respectively.

	Additive genetic architecture				Non-shared environment architecture			
	1991	1995	1997	2002	1991	1995	1997	2002
1991	1.00	.90	.80	.49	1.00	.17	.12	.05
1995	.76	1.00	.89	.54	.20	1.00	.34	.15
1997	.63	.82	1.00	.61	.12	.32	1.00	.22
2002	.39	.52	.63	1.00	.05	.15	.21	1.00

DISCUSSION

This is the first study that examined genetic and environmental contributions to stability over time of OC symptoms in adults. We found that OC symptoms are moderately stable across time with correlations of around .4 between measurement occasions. In contrast to the modest longitudinal phenotypic correlations, the longitudinal genetic correlations were substantially higher. We observed genetic correlations between roughly .4 and .9, with most genetic correlations varying around .8. So, the main reason for stability of OC symptoms was that the genetic influences on OC symptoms are stable across time. This means that to a large extent the same genes are expressed across time.

The moderate phenotypic stability seems in line with the clinical papers, which presented a more optimistic view of the course of OCD (Orloff *et al.*, 1994; Skoog & Skoog, 1999; Steketee *et al.*, 1999; Angst *et al.*, 2004; Reddy *et al.*, 2005). These studies suggested a relatively favourable course and outcome of OCD that is otherwise considered to be a chronic illness with waxing and waning course. Our results support the notion that having OC symptoms at one age does not automatically imply having OC symptoms for the rest of one's life.

Interestingly, in our paper examining stability for OCS in children (van Grootheest *et al.*, 2007a), we came to the same conclusion, but one big difference appeared between the two studies. Where genetic factors explained 70% of the stability in adults, in children a percentage of around 40% was found. In children, part of the stability was also due to common environmental factors shared by children growing up in the same house. These influences are not seen in adults. Although phenotypic stability is roughly the same in children and adults, the causes of stability differ. The influence of genes on stability is more important in adults than in children and environmental factors are of more importance in children than in adults. We also found that there is little transmission of unique environmental factors. This means that, on a population level, individual experiences have limited impact on the stability of OC symptoms in adults.

We found sex-differences in OC symptom scores at three time-points, but not at the last time-point. For the last time-point we used the PI-R ABBR, instead of the YASR-OCS. So the diminishing sex differences in OC-symptoms scores could well be caused by the use of a different measurement, although the possibility that the sex differences are age-dependent cannot be excluded. As longitudinal prevalence studies are scarce, we cannot compare these results with other studies. However, the results are in line with several studies which found no sex-differences or at the highest a slight preponderance for women having OCD (Nestadt *et al.*, 1998; Crino *et al.*, 2005; Torres *et al.*, 2006).

With the simplex model we were able to estimate the variance associated with measurement error. Around 25% of the total variation of OC symptoms was accounted for by measurement error. This means that 75% of the variation is "true" variance due to genetic and environmental effects. This means that, after correcting for measurement errors, genetic factors account for more than 50% of this variation.

Additive genetic factors are mainly responsible for the stability of OC symptoms. Even more important is the finding from the simplex model that in general the same genes account for OC symptoms at different ages. Genetic innovations are apparent but small, except at the last time-point, when the PI-R ABBR is used. It implies that the YASR and the PI-R ABBR questionnaires, besides measuring a partly similar concept of OC symptoms, are measuring different information of OC symptoms. As both questionnaires are different in several ways, this is not surprising. It again emphasizes the need to use different questionnaires at the same time, as every questionnaire has its merits and demerits and captures other pieces of information about the OC phenotype.

Although we found differences in variances for men and women, the proportions of variances and general architecture of the longitudinal analyses are remarkably similar. Taking in account earlier research, where we concluded that the same genes accounted for OC symptoms in men and women (van Grootheest *et al.*, 2007b) plus the existence of stable genetic factors, it would imply that data of men and women at different ages can be pooled together in molecular genetic research projects, obtaining an increase of power. In the near future, we intend to conduct QTL linkage analyses using the data of the current study, gaining power by using multivariate techniques that analyze pleiotropic action of the QTL on several variables (Boomsma, 1996). The factor structure for the QTL will be parameterized in terms of a simplex process, consisting of a innovation parameter at the first time-point and transmission parameter between the different time-points (Evans, 2003).

The results of this study should be interpreted in the context of four potential limitations. First, although both the YASR-OCS and PI-R ABBR show both a moderately high sensitivity and specificity in diagnosing DSM-IV OCD, the genetic and environmental contributions presented in this report reflect OCS scores, not clinical measures of DSM-IV OCD. Because of the relatively low prevalence of OCD, twin studies rely on dimensional measures with the underlying assumption that OCD reflects the end of a normal distribution, while OC symptoms represent a milder form of the latter (Jonnal *et al.*, 2000; van den Oord *et al.*, 2003; Kendler, 2005).

Second, the YASR-OCS and PI-R ABBR were used in a longitudinal design without any knowledge about the relationship between the measurements cross-sectionally. Both measurements were developed to screen for OC symptoms and both show good psychometric properties, but the correlation between the measurements has yet to be established. However, in view of the fact that the estimates of the proportions of variance at different time-points are very stable and that genetic correlations are moderate, we expect that both questionnaires are measuring mainly the same underlying liability to OCS, with the PI-R ABBR capturing some extra information.

Third, both the YASR-OCS and PI-R ABBR showed a skewed distribution. One could use a threshold model to deal with this problem, but the disadvantage of a threshold model is the loss of power (Derks *et al.*, 2004). Therefore, we used continuous scales with the disadvantage of possibly underestimating the twin and longitudinal correlations, resulting in underestimating the genetic contributions to OCS.

Fourth, the use of twin models requires several assumptions, including the absence of assortative mating, the equal environment assumption, and the absence of gene-environment interaction and correlation. Van Grootheest *et al.* (2008) found small, but significant assortative mating for OC symptoms but concluded that the bias in twin studies caused by the small amount of assortment is negligible. Jonnal *et al.* (2000) tested the EEA for OC symptoms and concluded that the EEA was not violated. Gene-environment interaction could affect twin similarity in either direction depending on whether both twins are exposed to the specific environmental factor in question; to our knowledge, gene-environment interaction and/or correlation have yet to be demonstrated for the phenotype studied here.

In summary, this study provides evidence from a large sample of twins that OC symptoms are moderately stable over time and this stability is strongly influenced by additive genetic factors. We did find high till moderate genetic correlations over time, suggesting that in general the same genes influence OC symptoms over time.

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CHAPTER 10

Environmental factors in obsessive-compulsive behavior: evidence from discordant and concordant monozygotic twins

Cath, D. C., van Grootheest, D. S., Willemsen, G., Van Oppen, P. & Boomsma, D. I. (2008). Environmental Factors in Obsessive-Compulsive Behavior: Evidence from Discordant and Concordant Monozygotic Twins. *Behavior Genet,* 38(2), 108-20.

Environmental factors in obsessive-compulsive behavior: evidence from discordant and concordant monozygotic twins

Cath, D. C., van Grootheest, D. S., Willemsen, G., Van Oppen, P. & Boomsma, D. I.

ABSTRACT

Background Research about environmental factors causing Obsessive-Compulsive symptoms is scarce. By using a discordant monozygotic twin design it is possible to investigate environmental factors that protect against or exacerbate OC symptoms.

Methods We selected 25 MZ twin pairs discordant, 17 MZ twin pairs concordant high and 34 MZ pairs concordant low on OC symptoms from a large longitudinal Dutch sample of adult twin pairs and their family members, applying stringent criteria for OC symptomatology. Data were collected on psychopathology, family structure, health, lifestyle, birth complications and life events. Unique environmental factors were studied using within-discordant MZ pair comparisons, whereas between-concordant MZ pair comparisons were used to study environmental factors that are shared by the twins of an MZ pair.

Results The high-scoring MZ twins of the discordant group reported more life events (especially sexual abuse) than their low-scoring twin-siblings. The between-pair comparisons showed lower birth weight in the discordant MZ pairs than in the concordant MZ pairs. Further, the concordant high MZ pairs as well as their spouses had a lower educational level than the two other groups. On scale scores of anxious-depression, neuroticism, and somatic complaints, concordant high MZ pairs showed highest scores, and the discordant MZ pairs scored intermediate, except for neuroticism, on which the high-scoring twins of discordant MZ pairs were equal to the twins of the concordant high pairs. Discordance on psychological scale scores between the concordant MZ pairs was evident from 1991 onward, and within the discordant MZ pairs from 1997 onward, confirming previous reports of an association of early-onset OC symptoms with higher genetic load.

Conclusions This study reports on both unique and shared environmental factors associated with OC - symptomatology. Whether these factors operate in addition to or in interaction with genetic disposition is to be elucidated in future studies.

Obsessive-Compulsive Disorder (OCD) is characterized by repetitive distressing and anxiety-provoking intrusive thoughts, mostly in combination with time-consuming repetitive actions designed to reduce tension or anxiety caused by the disturbing thoughts (American Psychiatric Association, 1994). OCD can run, especially if untreated, a chronic and disabling course (Nestadt *et al.*,1998). Family studies have quite convincingly shown that early-onset OCD is familial (Pauls *et al.*,. 1995; Nestadt *et al.*, 2000). Studies in 7-12 year old twins have indicated that between 47% and 58% of the variance in Obsessive Compulsive (OC) behavior is explained by additive genetic factors (Hudziak *et al,*. 2004). The remaining variance is almost entirely explained by unique environment, with a small contribution of shared environmental factors (16%) at age twelve In adults, twin studies have indicated a more modest contribution of genetic factors (van Grootheest *et al.*, 2005) . One twin study in women suggested heritability of 33% and 26% respectively for obsessions and compulsions (Jonnal *et al.*, 2000). Further, a recent twin study in 5893 mono- and dizygotic twins, and 1304 additional siblings from the population-based Netherlands Twin Register (Boomsma *et al.*, 2002), indicated heritability estimates of 47% for both men and women (van Grootheest *et al.*, 2007).

The course of OCD is moderately stable: longitudinal twin studies as well as epidemiological and clinical studies have indicated that on average 50% of cases remit over time (van Grootheest *et al.*, 2007; Angst *et al.*, 2004; Skoog & Skoog, 1999). Environmental factors explain about half of persistence in boys and two-third of persistence in girls Thus, environmental factors are of substantial importance in the likelihood to obtain and persist or remit with respect to OC symptomatology.

To date, only few studies have addressed the specific nature of these environmental factors in OC phenomenology. Which environmental influences can be detected from the literature? Family studies have revealed that parents of children with OCD suffer from poorer mental health and have fewer coping strategies than parents of healthy children (Derisley *et al.*, 2005). A-specific risk factors for (the persistence of) OCD include: earlier age at onset, presence of co-morbid conditions and low socio-economic status (Skoog & Skoog, 1999; Stewart *et al.*, 2004; 2005; Angst *et al.*, 2004). Further, OCD patients report more often than healthy controls to have been overprotected or emotionally neglected by their parents (Cavedo & Parker, 1994). Patients with the hoarding subtype of OCD in particular, report a lack of parental emotional warmth (Alonso *et al.*, 2004). Perinatal risk factors, such as prolonged labour and edema during pregnancy, have been reported to increase the risk of later OCD (Vasconcelos *et al.*, 2006). Childhood sexual abuse appears to be an important mediator for later OCD, especially in women (Lochner *et al.*, 2002). The relationship between religiosity and OCD is unclear. Some authors find increased frequencies of religious obsessions and hand washing among highly religious protestants in comparison with less or non-religious subjects (Abramowitz *et al.*, 2004), while others find no relation between religiosity and an increase in OC symptoms (Assarian *et al.*, 2001), and argue that religiosity is merely a form in which OC symptoms can be displayed (religious obsessions) (Tek & Ulug, 2001). Finally, ß-haemolytic streptococcal infections have been reported to be associated with OC symptom exacerbation (March *et al.*, 1990).

The comparison of monozygotic (MZ) twins who score high on a trait with their low-scoring co-twins, comprises a powerful method to identify environmental factors involved in a disorder (Martin *et al.*, 1997). MZ twins have identical genomes and are born and raised at the same time in the same family, thus sharing a very similar family environment. Consequently, discordance on the trait is mostly explained by differences in the non-shared (i.e., *unique*) environment that act either directly on the phenotype, or by epigenetic mechanisms (Fraga *et al.*, 2005). Environmental factors that are *shared* by both members of a twin pair (such as maternal smoking during pregnancy, or parental divorce) can be studied by comparing MZ twins who are concordant high on the trait with MZ twins who are concordant low.

Comparisons within discordant MZ pairs or between concordant MZ pairs have not been employed to study environmental factors involved in OC phenomenology. In other psychiatric disorders, such as schizophrenia and ADHD (Stabenau and Pollin, 1993; Lehn *et al.*, 2007), as well as in somatic disorders such as diabetes mellitus (Bo *et al.*, 2000)., this method has been successfully used One twin study on a disorder related to OCD, i.e. Gilles de la Tourettes' Syndrome (GTS), has studied basal ganglia D2-receptorbinding in 5 MZ twins who were discordant on tic severity, and found that caudate nucleus D2 receptor binding increased by up to 17% in the more severely affected twins when compared with their less severely affected twin siblings (Wolf *et al.*, 1996). This within MZ twin discordance reflects unique environmental influences on D2-caudate receptor density.

In this study, we used prospective data of adult twins from the Netherlands Twin Register, who have been followed between 1991 and 2002, and about whom information on a wide range of variables was collected every 2-3 years (Boomsma *et al.*, 2000). Differences between the MZ concordant and discordant groups were described using measures of anxiety and depression co-occurring with OC behavior. The aim of this explorative study was to replicate and extend the information from previous studies on both unique and shared environmental influences that might protect against or exacerbate OC behavior. Unique environmental factors were studied using within discordant MZ twin pair comparisons. To study environmental factors shared by both twins of a pair, between-MZ pair comparisons were used. Parent data on level of education and on drinking and smoking behavior were used to compare the groups of twin pairs on these common environment influences. Further, measures of anxiety, depression and personality were compared between the parents of the concordant and discordant twin pairs, with the following reasoning: concordance between MZ twin pairs on OC behavior most likely results from genetic similarity between the twins of a pair. Thus, the contrasts between twin pairs who are concordant high and low reflect differences in genetic vulnerability to OC behavior. As a consequence, the parent scores on OC symptoms, on anxious depression and on neuroticism (the latter characteristics are known to be related to OC symptoms) are expected to reflect these differences in genetic vulnerability and therefore to be highest in the parents of the concordant high MZ pairs, to be intermediate in the parents of the discordant MZ pairs and to be low in the parents of the concordant low MZ pairs.

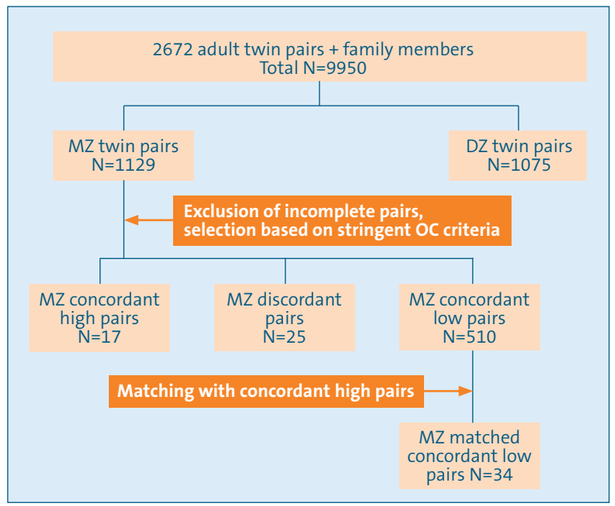
Finally, longitudinal measures of psychopathology were studied to investigate age at onset of OC symptoms, anxiety and depressive symptoms in the concordant and discordant groups. Family studies have suggested that lower age at onset is associated with higher familiality, possibly reflecting higher genetic load (Delorme *et al.*, 2005). We hypothesized that the concordant high MZ twin pairs, in whom the OC symptoms are theoretically more genetically determined, would show lower age at onset than the high scoring twins of the discordant group in whom unique environmental factors might be more important.

METHOD

Sample selection (figure 1)

The data of this study originate from a longitudinal study in twin families registered with the Netherlands Twin Register (NTR) (Boomsma *et al.*, 2002). Since 1991, twins and their families received a survey by mail every two to three years containing questionnaires about health, personality, life events, perinatal circumstances and lifestyle. The 2002 survey formed the starting point of this study., The Padua Inventory Abbreviated (PI-R ABBR) was added to the 2002 wave of data collection and was derived from the Padua Inventory-Revised version (PI-R), a widely used self report inventory on obsessive-compulsive symptoms (Sanavio, 1988; van Oppen *et al.*, 1992). The PI-R is a 41-item self-report instrument that measures OC symptoms on a 0-4 scale, and contains 5 subscales: washing, checking, rumination, precision and impulses (van Oppen *et al.*, 1995). It has been validated in the Netherlands, shows good psychometric qualities, and moderately correlates with the Y-BOCS symptom checklist, a clinician-derived checklist on OC symptoms (Denys *et al.*,. 2004). For the purpose of this epidemiological twin study, the PI-R was reduced to 12 items. Item choice was based on 2 items of each subscale with highest factor loadings in a previous validation study (van Oppen *et al.*, 1995), and with one additional item for each of the more equivocal obsession subscales: rumination and impulses. The PI-R ABBR is shown in table 1. To investigate its psychometric qualities psychometric analyses have been conducted in three groups derived from an earlier study by Van Oppen *et al.* (1995). These groups encompassed a population-based control group (n = 428), a psychiatric control group (n = 272) and a clinical OCD group (n = 120); for an extensive description of the study groups (see van Oppen *et al.*, 1995). Cronbachs' α of the scale was 0.73, which is an indication of good internal consistency. Analyses of Variance (ANOVAs) of PI-R ABBR scores within the 3 groups revealed a significant main between-group effect ($p < .0001$). Post-hoc t-tests showed that the mean PI-R ABBR-OC score for the OCD group (20.7 ± 8.1) was significantly higher than scores of the psychiatric control group (12.4 ± 7.4) as well as the population control group (6.6 ± 5.6; $p < .0001$ in both comparisons). To investigate whether the PI-R ABBR can accurately screen for OCD, and to establish cut-points of OC behavior, Receiver Operating Characteristic (ROC) analyses were carried out. ROC analyses use the association between sensitivity and specificity to derive an Area Under the Curve (AUC), which indicates how well a measure distinguishes between case positives (i.e., OCD group) and case negatives (i.e., psychiatric controls or population controls) irrespective of the base rate. A value of .50 of the AUC indicates chance level and 1.0 indicates a perfect diagnostic tool (Swets, 1996; McFall and Treat, 1999). The AUC for the PI-R ABBR. when compared with clinical controls was .78 (95% CI = .73 - .83). When compared with the population controls, the AUC was .93 (95% CI = .90 - .95). At the best cut-off point of 16 (i.e., maximum difference between sensitivity and 1-specificity), the sensitivity was .74 with a specificity of .72, when compared with clinical controls.

Figure 1. The 2002 NTR wave using the PI-R abbreviated



Of the adult twins, 2672 pairs, their family members and – in some instances - their spouses (a total of 9950 individuals) returned the survey. Monozygotic twin pairs were selected on the basis of high or low scores on the PI-R ABBR. Using the stringent criteria derived from the analyses described above, discordant, concordant high and concordant low MZ twin pairs were selected. Twin pairs were considered to be discordant when one twin scored > 17 (in the clinical range), and his/her MZ twin sibling scored < 7 (population control range). Pairs were considered to be concordant high when both twins scored > 17, and concordant low when both twins scored < 7. Information on zygosity from DNA polymorphisms was available in 19 MZ twin pairs (25%) of the final sample. When DNA polymorphisms were not available zygosity was determined from questions about physical similarity of the twins and confusion of the twins by family members, friends and strangers. Overall, agreement between zygosity diagnoses based on questionnaire and DNA data is 97% (Willemsen *et al.*, 2005). After exclusion of incomplete pairs, 25 MZ discordant pairs, 17 MZ concordant high pairs and 521 MZ concordant low pairs were identified. Concordant low pairs were matched on age and sex with concordant high pairs and oversampled, so that 34 concordant low pairs were finally retained.

Table 1. The Padua Inventory-Revised abbreviated (PI-R ABBR)

	PI-R ABBR	Original Factor
1	In certain situations, I am afraid of losing my self-control and doing embarrassing things	Impulses
2	I check and recheck gas and water taps and light switches after turning them off	Checking
3	I feel obliged to follow a particular order in dressing, undressing and washing myself	Precision
4	When I see a train approaching I sometimes think I could throw myself under its wheels	Impulses
5	I return home to check doors, windows , drawers etc., to make sure they are properly shut	Checking
6	When I start thinking of certain things, I become obsessed with them	Rumination
7	I feel I have to repeat certain numbers for no reason	Precision
8	Unpleasant thoughts come into my mind against my will and I cannot get rid of them	Rumination
9	My thoughts constantly go astray, therefore I find it difficult to attend to what is happening around me	Rumination
10	I sometimes have to wash or clean myself dimply because I think I may be dirty or 'contaminated'	Washing
11	I get upset and worried at the sight of knives, daggers and other pointed objects	Impulses
12	If I touch something which I think is 'contaminated', I immediately have to wash or clean myself	Washing

Of the final 76 MZ twin pairs selected for this study, 18 pairs participated in wave 2002 only, 28 pairs participated in two waves, 4 pairs in three, 8 pairs in four, 13 pairs in five, and 4 pairs in all six waves.

Measures and instruments

The NTR survey contains a broad range of longitudinal measurements taken at six time points between 1991-2002, as well as cross-sectional measurements. Information is obtained on life events, perinatal adversities, physical and mental health, lifestyle factors such as physical activity, religiosity, drinking, smoking and drug behavior, and on demographic variables such as relationships, number of children, level of education, living situation, and work status. Since this is an exploratory study, all available information was taken into account.

Religiosity was assessed by asking whether the respondent had had a religious upbringing (yes/no), the person's current religion, and whether the respondent currently was an active church member.

On alcohol and smoking behavior, respondents were questioned about their consumption ever, in the past year and past month, as well as the number of cigarettes or glasses of alcohol per week Alcohol dependence was assessed by the CAGE (4 questions) (Bush *et al.*, 1987).

The occurrence of negative life events throughout the lifespan was measured in the 2002 survey, using an adapted version of the Dutch life event scale (Schokverwerkings Inventarisatie Lijst = SchIL) (van der Velden *et al.*, 1992). This scale gathers information on: death of a spouse, father, mother, child, sibling or significant other; serious illness or injury of self or a significant other; divorce/break-up of a relationship; traffic accident; violent and sexual assault or rape, and robbery. Response categories are: never experienced; 0-6 months ago; 6-12 months ago; 1-5 years ago, and more than five years ago.

Data on anxiety and depression were available at most time points between wave 1 and 6, and were assessed with: the Spielberger State-Trait Anxiety Inventory, trait scale (Spielberger *et al.*, 1979; Van der Ploeg, 1979), and the Young Adult Self report, anxious-depressed subscale (Achenbach, 2000; Verhulst *et al.*, 1997). Questionnaires between waves 1 and 4 (between 1991 and 1997) also contained the 8-item OC symptom subscale of the YASR (Nelson *et al.*, 2001; Geller *et al.*, 2006). Neuroticism, somatic complaints and extraversion were measured with the Amsterdamse Biografische Vragenlijst (ABV; Amsterdam Biographical Questionnaire) (Wilde *et al.*, 1964). The ABV neuroticism and extraversion scales are very similar to the Eysenck Personality Questionnaire neuroticism and extraversion subscales (Eysenck and Eysenck, 1964), and contain answer categories: yes/no/don't know. The satisfaction with life scale and the subjective happiness scale (Lewis and Joseph, 1995), a combined 10-item scale with scoring possibilities between 1 and 7 were taken, and the Rosenberg self-efficacy scale, a 10-item scale scoring between 1 and 4 (Rosenberg, 1965; Helbing, 1982).

Socio Economic Status (SES) in 2002 was assessed using a full description of the occupation of the twins according to the descriptions provided by the Central Office for Statistics in the Netherlands. The work level was coded into 3 levels based on the mental complexity of the work, ranging from low skilled (1) to academic work (3). Living situation was coded between 1 and 3 (1 = with parents; 2 = alone; 3 = with partner).

Finally, we used child-derived information on their parents' level of education. Direct parent information was used to collect information on their smoking and drinking behavior and on their scores of OC behavior, anxiety and depression.

Statistical analyses

Within-pair analyses. Within-discordant pair differences between the high and low-scoring twins on the PI-R ABBR were calculated using paired t-tests (t-tests

for two related samples) for continuous data, Wilcoxon signed- rank tests for ordinal data and McNemar X^2 tests of matched pairs for nominal data.

Between-pair analyses

Variables that measure psychological health, as well as measures of environmental influences on OC symptoms were compared between the concordant high, the concordant low and the discordant MZ twin pairs, using one-way ANOVAs for continuous data, Kruskal-Wallis tests for ordinal data and X^2 tests for nominal data. Post-hoc comparisons were conducted using post-hoc Scheffé's (continuous data) and Mann-Whitney-U tests (ordinal data). Post-hoc Scheffé testing, although more liberal than Bonferroni correction, provide some correction of type I error. Two-tailed probabilities were used in all analyses, since we had no clear expectation of the direction of the findings.

To adjust for correlated error in the between-group comparisons of common environment variables, separate regression analyses (multiple regression for continuous measures and logistic regression for categorical measures) were conducted in STATA 9.2 for these variables (StatCorp, College Station, Texas, USA). The robust cluster option was used to account for nonindependence of the twin pairs on the variables that reflected common environmental influences (i.e. caesarean section, birth weight, and religious upbringing of the twin; parental death and divorce, death of a sibling, and level of education, alcohol use and smoking behavior of the parents. Alpha was set at 0.05.

RESULTS

WITHIN-PAIR ANALYSES OF DISCORDANT PAIRS

Twenty-five MZ twin pairs discordant on OC behavior were included, of whom 18 pairs were female. Their mean age was 29.6 years (SD 6.8 years). Mean PI-R ABBR scores in the high scoring twins of the discordant pairs were 21.4 (SD 5.9), in the low scoring twins 4.5 (SD 2.0).

Table 2. Within-Discordant twin pair characteristics

	Discordant low OC twin Mean (SD)	Discordant high OC twin Mean (SD)	p-value
Birth weight (g)	2189 (806)	2028 (667)	n.s.
Birth order (first born)	n=10	n=14	n.s.
General health (1-5)	4.1 (0.7)	3.8 (0.6)	0.03
Mental health contacts ever yes	n=7	n=9	n.s.
Sumscore impediments physical activity	43.5 (12.5)	53.9 (12.4)	<0.001
Number of persons drinking ever	n=23	n=23	n.s
N drinks per wk (past 12 months)	11.1 (1.4)	13.4 (0.7)	n.s.
CAGE score alcohol dependence	4.0 (0.2)	4.3 (0.7)	n.s.
Duration current relation (yrs)	5.9 (7.4)	3.0 (0)	n.s.
Number of children	1.1 (1.2)	0.7 (0.6)	n.s.
Education level self (1-13)	7.9 (3.0)	8.3 (2.6)	n.s.
Education level partner (1-13)	8.3 (3.6)	8.1 (3.1)	n.s.
Living situation (1-4)	2.8 (0.8)	2.7 (0.8)	n.s.
PI-ABBR OC scale	4.5 (2.0)	21.4 (5.9)	<0.001
YASR anxious depression scale	4.3 (2.8)	11.6 (4.3)	<0.001
ABV extraversion	51.0 (16.7)	45.6 (12.5)	n.s.
ABV neuroticism	48.6 (23.1)	85.3 (27.4)	<0.001
ABV somatic complaints	16.6 (5.1)	24.4 (10.3)	<0.001
STAI-trait	31.6 (4.7)	46.4 (10.8)	<0.001
Satisfaction with life scale scores	27.4 (4.1)	23.8 (7.0)	0.02
Happiness scores	22.7 (3.9)	17.9 (5.8)	0.001
Self-efficacy scores	31.3 (4.0)	27.5 (4.7)	0.006

PI-ABBR, Padua Inventory Revised Abbreviated; OC, obsessive-compulsive; YASR, Young Adult Self Report; ABV, Amsterdamse Biografische vragenlijst; STAI, State trait Anxiety Inventory; SBL, Spannings behoefte Lijst (sensation seeking list); SD, Standard Deviation; n.s., not significant

Health and lifestyle characteristics (table 2)

High-scoring twins of the discordant pairs experienced lower general health ($p = 0.03$) and more impediments in physical activity ($p < 0.001$) than the low-scoring co-twins. The duration of the current relationship of the high-scoring twins tended to be shorter ($p = 0.06$), and they tended to have fewer children ($p = 0.07$). They were less satisfied with life ($p = 0.02$), less happy ($p = 0.001$) and had lower self-efficacy scores ($p = 0.006$). They showed no differences with respect to birth weight, birth order, church participation, drinking or smoking behavior, nor on level of education, work status, living situation, or number of (mental) health contacts. The high-scoring twins of the discordant pairs scored significantly higher on the YASR anxious-depressed subscale ($p < 0.001$), on the neuroticism subscale ($p < 0.001$), on the ABV subscale of somatic complaints ($p < 0.001$), and on STAI-trait ($p < 0.001$). On the ABV extraversion scale, no within-pair differences were found.

Table 3. Within-discordant twin comparisons for unique life eve

	Discordant low OC twin Mean (SD)	Discordant high OC twin Mean (SD)	p-value
Birth weight (g)	2189 (806)	2028 (667)	n.s.
Disease self (0-2)	0.08 (0.4)	0.26 (0.6)	n.s.
Disease child (0-2)	0.09 (0.4)	0.6 (0.1)	n.s.
Disease partner (0-2)	0.09 (0.4)	0	n.s.
Disease significant other (0-2)	0.82 (0.9)	0.82 (0.9)	n.s.
Death child (0-2)	0	0	n.s.
Death partner (0-2)	0	0	n.s.
Death significant other (0-2)	1.1 (0.9)	1.0 (0.9)	n.s.
Sexual abuse (0-2)	0.17 (0.5)	0.43 (0.8)	**0.08**
Violence (0-2)	0.17 (0.6)	0.17 (0.6)	n.s.
Relationship termination (0-2)	0.52 (0.8)	0.82 (0.9)	n.s.
Theft (0-2)	0.47 (0.8)	0.56 (0.8)	n.s.
Traffic accident (0-2)	0.52 (0.8)	0.38 (0.7)	n.s.
Dismissal (0-2)	0.30 (0.7)	0.48 (0.7)	n.s.
Total score life events	2.35 (1.9)	2.76 (1.7)	n.s.

SD, Standard Deviation; n.s., not significant

Unique environment influences (table 3)

The only within-pair difference found on unique life events, was the tendency of the high-scoring twins of the discordant pairs to have experienced more sexual assault than the low-scoring twins ($p = 0.08$). All persons who had experienced sexual assault were women. Two low-scoring twins of the discordant pairs reported on sexual assault, versus 5 high-scoring twins. The low-scoring twins and 4 of the 5 high-scoring twins of the discordant pairs reported to have experienced the assault more than 5 years ago, versus 1 twin who had experienced sexual abuse between 1 and 5 years ago.

Longitudinal data

YASR-OC subscale scores, taken in 1991, 1995 and 1997, revealed significant differences between high and low-scoring twins of the discordant pairs in 1997 ($p = 0.007$). Further, scale scores between 1991-2002 revealed significant within-pair differences on the YASR anxious-depressed subscale from 1997 onward ($p = 0.001$), on the neuroticism subscale from 1993 onward (p between 0.01 and < 0.001 at wave 2-5), on the ABV subscale of somatic complaints from 1997 onward (p between 0.015 and < 0.001), and on STAI-trait scores from 1997 onward (p's between 0.007 and < 0.001).

BETWEEN-PAIR ANALYSES OF CONCORDANT AND DISCORDANT PAIRS

Seventeen MZ twin pairs were included who were concordant high on OC behavior, of whom 14 pairs were female. Their mean age was 30.0 years (SD 11.2 years), mean PI-R ABBR OC scores were 23.7 (SD 6.7). Thirty-four MZ twin pairs were included who were concordant low on OC behavior, of whom 28 pairs were female. Their mean age was 30.0 years (SD 11.3 years), mean PI-R ABBR OC scores were 3.8 (SD 2.2).

Health and lifestyle characteristics (table 4)

The concordant low group generally experienced the best health, with the discordant group scoring intermediate between high and low concordant groups. Members of the discordant group more often had a spouse than the concordant high group, and were living with a spouse more often than both concordant groups. No between-group differences were found for smoking behavior. For drinking behavior, the concordant high group showed the highest scores on alcohol dependence ($p = 0.02$ and 0.04 in comparison with the concordant low and discordant group), although they scored intermediate between the low and discordant groups on current number of drinks per week. On religious upbringing, there were no significant differences between the study groups. Interestingly, the concordant low MZ twin pairs, as well as their spouses, reported to have a higher level of education than the concordant high and discordant twin pairs (p's 0.02 in both comparisons).

On life events, the concordant high MZ twin pairs reported more often that they had been dismissed from work than the concordant low scoring pairs ($p = 0.04$), with the discordant pairs scoring between the concordant high and low pairs. Further, the discordant pairs reported more often to have been sexually assaulted in comparison with both the concordant low and high-scoring pairs; $n = 7$ individuals in the discordant group versus $n = 0$ and $n = 1$ individual in the concordant high and low groups ($p = 0.02$ and 0.03 respectively).

Table 4. Between concordant and discordant twin pair comparisons for health and lifestyle characteristics

	Concordant low twin pairs Mean (SD)	Concordant high twin pairs Mean (SD)	Discordant twin pairs Mean (SD)	Low-High p-value	Low-discordant p-value	High-discordant p-value
General health (1-5)	4.4 (0.7)	3.6 (1.2)	4.1 (0.7)	<0.001	0.007	n.s.
Mental health contacts ever yes	N=8 (12%)	N=21 (61%)	N=16 (32%)	<0.001	0.006	0.009
Impediments physical activity	41.3 (12.6)	53.0 (17.1)	43.5 (12.5)	0.001	n.s.	0.03
Specialized medical treatment ever yes	N=11 (16%)	N=15 (44%)	N=11 (22%)	0.002	n.s.	0.04
Currently active in church (1-3)	0.8 (0.7)	0.5 (0.7)	0.9 (0.8)	n.s.	n.s.	n.s.
Number of persons drinking ever	N=62 (91%)	N=19 (56%)	N=35 (70%)	n.s.	0.003	n.s.
N drinks per wk (past 12 months)	2.7 (1.4)	2.3 (1.5)	1.9 (1.2)	n.s.	0.01	n.s.
CAGE score alcohol dependence	4.1 (0.5)	4.5 (0.8)	4.2 (0.5)	0.02	n.s.	0.04
Number of persons smoking ever	n=20 (29%)	n=14 (41%)	n=18 (36%)	n.s.	n.s.	n.s.
Number of cigarettes per day (1-7)	4.1 (1.1)	4.7 (1.1)	3.8 (1.0)	n.s	n.s.	0.07
N persons with partner	N=41 (60%)	N=17 (50%)	N=35 (70%)	n.s.	n.s.	0.04
Children yes	N=16 (23%)	N=8 (23%)	N=25 (50%)	n.s.	0.003	0.015
Education level self (1-13)	9.4 (2.3)	8.27 (2.8)	8.24 (2.8)	0.02	0.02	n.s.
Education level partner (1-13)	9.1 (2.8)	6.7 (3.7)	8.20 (3.4)	0.006	n.s.	n.s.
Living situation (1-3)	2.4 (0.8)	2.2 (1.0)	2.8 (0.8)	n.s.	0.04	0.01
PI-R ABBR OC scale	3.8 (2.2)	23.7 (6.7)	12.9 (9.5)	<0.001	<0.001	<0.001
YASR anxious depression scale	2.9 (4.7)	14.5 (19.3)	8.7 (12.6)	<0.001	<0.001	<0.001
ABV extraversion	62.8 (16.2)	46.4 (17.7)	48.3 (17.7)	<0.001	<0.001	0.001
ABV neuroticism	36.2 (18.9)	92.8 (19.7)	66.6 (31.1)	<0.001	<0.001	n.s.
ABV somatic complaints	15.7 (3.7)	27.5 (8.3)	20.3 (8.8)	<0.001	0.003	<0.001
STAI-trait	29.4 (6.4)	36.9 (7.9)	37.6 (7.5)	<0.001	<0.001	<0.001
Satisfaction with life	28.7 (4.0)	19.8 (7.2)	25.6 (5.9)	<0.001	0.01	0.001
Happiness	24.2 (3.2)	16.2 (5.7)	20.4 (5.4)	<0.001	<0.001	0.01
Self-efficacy	33.7 (3.9)	25.5 (3.9)	29.4 (4.7)	<0.001	<0.001	<0.001

PI-ABBR, Padua Inventory Revised Abbreviated; OC, obsessive-compulsive;YASR, Young Adult Self Report; ABV, Amsterdamse Biografische vragenlijst; STAI, State Trait Anxiety Inventory; SD, Standard Deviation; n.s., not significant

Finally, the discordant pairs reported more traffic accidents than the other groups (p = 0.05 and 0.02 when compared with the concordant low and high pairs respectively).

On psychological scale scores, the concordant high group scored, as expected, overall higher on the PI-R-ABBR (p's < 0.001), the YASR anxious-depressed scale (p's < 0.001), ABV neuroticism (p < 0.001 in low-high comparison; p = n.s. between high and discordant twin pairs), somatic complaints (p's between < 0.001 and 0.003), and STAI-trait anxiety (p's < 0.001). Further, the concordant high group had lower scores on ABV extraversion (p's 0.001), satisfaction with life (p's between 0.01 and 0.001), happiness (p's between 0.01 and < 0.001) and self-efficacy (p's < 0.001) than the concordant low and discordant groups.

Shared environment influences (table 5)

Between-group analyses revealed that the discordant group had the lowest rate of cesarean sections (p's of 0.005 and 0.006 in comparison with the concordant low and high groups), while there was no difference between the concordant groups. The discordant group had the lowest birth weight (p = 0.008 compared with the concordant low pairs and p < 0.001 compared with the concordant high pairs). There were no between-group differences on level of education of the parents (ps = non significant in all comparisons). There were no between-pair differences in the occurrence of parental death. The concordant low MZ pairs reported most on death of a sibling (p = 0.05 between concordant low and high pairs). There were no between-group differences with respect to relationship termination of the parents. On both drinking and smoking behavior of the parents, surprisingly the concordant low parents reported more drinking than the discordant parents, although alcohol consumption as well as number of cigarettes was low on average.

Longitudinal data

YASR OC scale scores revealed significant differences between low and high-scoring twin pairs in the 1995 (p = 0.02) and 1997 wave (p < 0.001). YASR anxious-depressed scale scores revealed significant differences between the concordant low and high groups from 1991 on (p's < .05 in all comparisons). ABV extraversion scores revealed significant between-group differences from 1993 onward (p's between < 0.001 and 0.008), whereas ABV neuroticism scores revealed significant between–group differences at all waves (P's between 0.05 and < 0.001). ABV somatic complaints showed significant between-group differences from 1997 on (p's < 0.001).

Parent data (Table 6)

Parent data were available for 66 persons; the 34 parents of concordant low twin pairs had a mean age of 53.6 years (SD 5.9), a PI-R ABBR mean score of 5.2 (SD 3.8); 9 parents of concordant high twin pairs had a mean age of 51.6 years (SD 2.5), and a PI-R ABBR mean score of 11.7 (SD 3.8); and 23 parents of discordant twin pairs had a mean age of 57.5 years (SD 6.9) and a

Table 5. Between twin-pair comparisons: comparison of common environment characteristics (after correction for interrelatedness)

	Concordant low twin pairs Mean (SD)	Concordant high twin pairs Mean (SD)	Discordant twin pairs Mean (SD)	Low-high p-value	Low-discordant p-value	High-discordant p-value
Cesarian section (yes)	N=5 pairs	N=3 pairs	N=0 pairs	n.s.	0.008	<0.001
Birth weight (g)	2650 (876)	2685 (795)	2109 (736)	n.s.	0.004	0.009
Religious upbringing yes	N=45 (67%)	N=16 (47%)	N=34 (69%)	n.s.	n.s.	n.s.
Education level father* (1-13)	7.5 (4.0)	5.5 (3.7)	5.7 (3.5)	n.s.	n.s.	n.s.
Education level mother* (1-13)	6.3 (3.7)	5.2 (3.4)	4.7 (3.0)	n.s.	n.s.	n.s.
Death mother (0-2) yes	n=2 (3%)	n=3 (10%)	n=4 (8%)	n.s.	n.s.	n.s.
Death father (0-2)	n=12 (19%)	n=7 (24%)	n=6 (12%)	n.s.	n.s.	n.s.
Death sibling (0-2)	n=6 (10%)	n=0	n=1 (2%)	0.05	n.s.	n.s.
Relationship termination parents (0-2)**	n=4 (14%)	n=2 (25%)	n=1 (7%)	n.s.	n.s.	n.s.
N parents drinking (ever; yes)**	91%	100%	74%	0.06	n.s.	0.04
N drinks/wk parents (1-7)**	3.5 (4 drinks/wk)	2.7 (2-3 drinks/wk)	2.3 (1-2 drinks/wk)	n.s.	0.03	n.s.
N parents smoking ever (yes)**	71%	89%	48%	n.s.	0.06	0.07
N cigarettes/day parents (1-7)**	4 (6-10 cig/day)	5(11-20 cig/day)	5 (11-20 cig/day)	n.s	n.s.	n.s.

* reported by twin children and by parents ** direct parent data; SD, Standard Deviation; n.s., not significant

Table 6. Between-parents comparisons of psychological scales

	Parents concordant low Mean (SD)	Parents concordant high Mean (SD)	Parents discordant Mean (SD)	High-low p-value	Low-discordant p-value	High-discordant p-value
PI-R ABBR OC scale	5.2 (3.8)	11.7 (3.8)	9.9 (5.7)	0.002	0.002	n.s.
YASR anxious depression scale	4.5 (3.5)	11.7 (4.2)	7.7 (4.3)	<0.001	0.02	0.04
ABV extraversion	53.4 (17.5)	44.9 (12.9	62.4 (13.3)	n.s.	n.s.	0.02
ABV neuroticism	36.3 (25.3)	79.8 (26.5)	62.7 (13.3)	<0.001	<0.001	n.s.
ABV somatic complaints	16.3 (4.5)	21.2 (6.6)	26.9 (2.3)	0.01	<0.001	0.005
STAI-trait	29.5 (6.7)	44.1 (7.1)	47.7 (4.1)	<0.001	<0.001	n.s.
Satisfaction with life	28.1 (4.9)	18.6 (8.5)	25.5 (7.1)	0.001	n.s.	0.03
Happiness	23.5 (3.5)	16.3 (6.9)	15.1 (3.3)	<0.001	<0.001	n.s.
Self-efficacy	32.1 (3.8)	28.0 (4.2)	25.3 (2.6)	0.01	<0.001	n.s.

PI-R ABBR, Padua Inventory Revised Abbreviated scale; OC, obsessive-compulsive; YASR, Young Adult Self Report; ABV, Amsterdamse Biografische vragenlijst; STAI, State Trait Anxiety Inventory; SD, Standard Deviation; n.s., not significant

PI-R ABBR mean score of 9.9 (SD 5.7). Between-group analyses of psychological scale scores showed that the parents of the discordant pairs scored between the parents of the concordant low and high pairs on anxious depression, satisfaction with life, happiness and self-efficacy scales. On somatic complaints and extraversion they showed higher scores than the other groups. On the PI-R ABBR, STAI trait and neuroticism they scored equal to the parents of the concordant high groups.

DISCUSSION

The most important aim of this MZ twin study has been to explore unique and shared environmental factors involved in OC symptoms.

Unique and shared environmental factors

The within-twin pair comparisons of the MZ discordant pairs were primarily used to study *unique* environmental factors associated with OC symptoms. Although the discordant pairs were genetically identical, were raised at the same time in the same family, and were selected from an epidemiological sample, the twins differed substantially on several measures across time. The twins who scored low on OC symptoms reported to feel healthier, to be more satisfied with life, happier and more self-efficient than their high scoring MZ twin siblings. They tended to have longer relationships and more children. Further, they had lower scores on anxious depression and on neuroticism, mostly from 1997 onward. The most striking unique environmental factor to explain these within-discordant pair differences was the relatively high frequency of sexual assault experienced by the high-scoring twins of the discordant pairs in comparison with their low-scoring twin siblings, which is in line with previous reports on this issue (Lochner *et al.*, 2004). However, two of the low-scoring twins of the discordant pairs reported on sexual assault as well, underscoring the complexity of presumed causality in the interplay between environmental and genetic factors in OCD. Interestingly, no sexual assault was reported by the concordant high-scoring MZ twin pairs. Thus, although the high-scoring respondents of the discordant pairs show similar OC symptomatology when compared with the concordant high MZ pairs, the pathways along which similar OC symptoms develop seem to differ between the high-scoring discordant twins on the one hand, and the high-scoring concordant pairs on the other. Although one can only speculate about causal relationships in this explorative study, the OC symptoms in the high-scoring twins of the discordant pairs seem to be associated more with environmental stressors (i.e. sexual assault) than are the OC symptoms in the concordant high-scoring pairs.

The between-twin pair comparisons to study environmental factors that are *shared* by the twins of a pair revealed low birth weight and low rates of caesarean section in the discordant pairs. We were unable to take the relationship between low birth weight and gestational age into account in the analyses, and were therefore unable to distinguish whether the study persons had been pre- or dysmature at birth. However, a recent twin study showed that low birth weight in itself resulted in an increase in problem behavior in later life (Wichers *et al.*, 2002). Children with low birth weight appeared to be more vulnerable to negative environmental factors than normal birth weight children possibly in association with a negative interaction between genetic vulnerability for problem behavior and low birth weight. Low birth weight can be indicative of a range of prenatal adversities such as maternal psychological stress, alcohol, drug abuse, or smoking during pregnancy. These adversities cause immunological challenge, and lead through various mechanisms to a diversity of psychopathology, including anxiety and depression (Meyer *et al.*, 2006; Huizink *et al.*, 2004; Nigg and Breslau, 2007). In this study, we did not find an indication of alcohol, smoking or drug abuse in the parents of the twin pairs, but other sources of prenatal stress can not be ruled out. Further, no discordant twin pairs were born through caesarean section, as opposed to 8 concordant pairs. This is remarkable in light of the fact that in general, caesarean section is carried out more often in multiple pregnancies, especially when one suspects low birth weight in the foetuses (Colla *et al.*, 2001). Although it might be a chance finding, one can speculate that – since caesarean section is intended to decrease perinatal adversities – the discordant group of this sample has been 'under treated', providing an additional negative environmental factor to explain between-group differences.

There were no between-group differences in rates of parental death or death of a sibling, nor in frequency of relationship termination between the parents, life events that reflect shared environmental stressors. In general, rates of these life events were low in this relatively young twin group, possibly hampering detection of between-twin pair differences. Alcohol use by the mother (especially during pregnancy) as well as maternal smoking is considered to be common environmental risk factors for problem behavior such as ADHD (Smidts, 2007). However, neither alcohol use nor smoking behavior of the parents was associated with OC symptoms in the concordant high or discordant groups of this study. Further, there was no association between OC symptoms and a religious upbringing in the study groups, which is in line with the literature on the lack of association between religiosity and OCD (Tek *et al.*, 2004), but deviates from reports of a protective effect of religion on other forms of psychopathology such as alcohol and drug abuse, depression and disruptive behavior (Kendler *et al.*, 1999). Apparently, different problem behavior is associated with different environmental risk factors.

Finally, level of education of the parents (as a measure of socio-economic status, a risk factor reported in OCD) was not found to be associated with OC symptoms in this study, although the parents of the twins who were concordant low on OC symptoms tended to have a higher level of education than the other groups, a difference that may have failed to reach significance due to the small sample size.

Finally, between- twin pair comparisons on unique life events revealed an elevated rate of dismissal in the concordant high-scoring twin pairs compared with the other pairs. Since dismissal typically represents a unique negative environmental influence on each twin of a pair, instead of being an environmental influence shared between the twins of a pair, its elevated rate among the high scoring concordant MZ pairs is better explained as being the consequence of OC symptomatology rather than causing OC symptoms; elevated dismissal rates in these OC twin pairs might result from over-scrupulosity and slowness in work -characteristics well known in OC symptomatology and subsequent dysfunction.

Health and lifestyle characteristics

Overall, as expected, the concordant low pairs reported highest scores of health, fewest mental and medical health contacts, and lowest scores on OC symptoms, anxiety and depression, neuroticism, and somatic complaints compared with the other groups. Further, they reported to be more extravert, more satisfied with life, happier and more self-efficient, with the discordant pairs scoring in between the concordant low and high pairs. On alcohol use, the concordant high-scoring twin pairs scored in between the low and discordant twin pairs over the past twelve months, with the number of drinks per week well below the quantity required to fulfil criteria for alcohol abuse or dependence according to DSM-IV criteria. However, subjective reports of alcohol withdrawal and dependence (CAGE scores) were increased in the high-scoring twin pairs compared with the low-scoring and discordant pairs. This might reflect increased scrupulosity and feelings of guilt, a well-known phenomenon in persons with OC symptoms, (Olatunji *et al.*, 2006), related to alcohol use and its toxic effects rather than a verifiable alcohol problem in the concordant high scoring MZ pairs.

A protective effect of level of education on OC symptoms was suggested by the finding of a higher level of education in the concordant low-scoring twin pairs than in the concordant high and the discordant twin pairs. Not only the concordant high scoring twin pairs but also their spouses had a lower level of education, which suggests that low level of education and OC symptomatology might share genetic vulnerability. Deficits in encoding complex information and subsequent memory impairments have been reported in OCD (Buhlmann *et al.*, 2006; Deckersbach *et al.*, 2000). These (genetically determined) impairments possibly mediate low educational level. On the other hand, low level of education in the concordant high-scoring group might be a consequence of the OC symptomatology in itself, a notion that is supported by the literature (Sorensen *et al.*, 2004).

The longitudinal data

As expected, the longitudinal data on OC symptoms, anxiety and depressive symptoms in the concordant and discordant groups revealed an earlier age at onset of OC and related symptoms in the concordant high group (from 1991 on) than in the discordant group (mostly from 1997 on). This confirms data from family-based studies where an earlier age at onset was associated with higher familial load (do Rosario-Campos *et al.*, 2005). Thus, assuming that OC symptoms in the concordant high-scoring twin pairs are more genetically mediated than in the discordant pairs, this study is in line with clinical studies indicating that age at onset might be an important phenotypic characteristic that

reflects differences in genetic characteristics underlying OCD (Delorme *et al.*, 2005).

The parent data

As parent scores on OC symptoms and related psychopathology were expected to reflect genetic vulnerability, we expected scores to be highest in the concordant high parents, to be intermediate in the discordant parents and to be low in the concordant low parents. On most measures of psychopathology, this assumption was confirmed. Thus, the intermediate scores in the parents of the discordant twins on OC, anxious-depression and neuroticism scales may be the consequence of the intermediate amount of genetic vulnerability to OC symptoms in this group. Therefore, these parent data suggest that the symptoms in the high-scoring twins of the MZ discordant group are likely to be the consequence of a moderate genetic vulnerability to OC pathology in addition to or in interaction with environmental mediators.

Limitations

First, sample size is small; although we sampled from a large group of MZ twins, only a small sample was retained due to the use of rigorous criteria. Consequently, especially in the within-discordant pair comparisons, some of the negative outcomes might in fact be the result of lack of power to detect within-pair differences. Alternatively we could have relaxed the stringent selection criteria, with the disadvantage of including twin pairs not scoring in the clinical range of OCD, thus representing an unclear group of problem behavior.

Second, considering the large number of tests relative to the small sample size, we only mildly corrected for type I errors. However, considering the exploratory nature of this study, an increase in the odds of type II errors by correction of type I errors was undesirable. Therefore, we decided to compromise by only applying a mild correction of type I errors (Perneger, 1998).

Finally, the database used in this study was not primarily designed to specifically inquire about environmental factors, leaving some questions unanswered, especially with respect to protective environmental mediators of OC symptomatology.

In conclusion, this study has been a first attempt to identify characteristics of the environment associated with OC symptoms using a twin study design. Some important environmental factors involved in OC symptomatology have been identified. Two crucial questions to be addressed in future studies are: 1) what is the differential impact of the various environmental mediators on OC symptoms, and under which circumstances and at which age are they most harmful? 2) Along which lines do the environmental factors found in this study operate? Do they add to genetic risk factors, are they causal in themselves, or do they operate through gene-environment interaction? Future studies are needed to study the differential effects of environment and genes on phenotypes (and endophenotypes), and to elucidate the nature of the interplay between genes and environment.

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CHAPTER 11

Heritability of Obsessive-Compulsive Symptom Dimensions

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Heritability of Obsessive-Compulsive Symptom Dimensions

van Grootheest, D. S., Boomsma, D. I., Hettema, J. M. & Kendler, K. S.

ABSTRACT

Background Recent research has shown that Obsessive-Compulsive Symptoms differ remarkably among patients and can be divided into several symptom dimensions. Obsessive-Compulsive Symptoms (OCS) are influenced by genetic components, but it is unknown to what extent these symptom dimensions are heritable. The phenotypic heterogeneity also raises the question to what extent the symptom dimensions are influenced by specific or shared genetic factors.

Methods We studied a population sample of 1383 female twins from the Virginia Twin Registry. OCS was measured by a questionnaire with 20 items from the Padua Inventory. After factor analysis, three reliable OC symptom dimensions were retained: Rumination, Contamination, and Checking. These OC dimensions were analyzed with multivariate genetic models to investigate both the overlap and uniqueness of genetic and environmental contributions underlying OC symptom dimensions.

Results The multivariate common pathway model provided the best description of the data. All symptom dimensions share variation with a latent common factor, i.e., OC behavior. Variation in this common factor was explained by both genes (36%) and environmental factors (64%). Only the Contamination dimension was influenced by specific genes and seemed to be a relatively independent dimension.

Conclusions The results suggest that a broad OC behavioral phenotype exists, influenced by both genes and non-shared environment. In addition, we found evidence for specific genetic and environmental factors underlying the Contamination dimension. Use of the Contamination dimension could therefore provide a powerful approach for the detection of genetic susceptibility loci that contribute to OCS.

In recent years, research on Obsessive-Compulsive Disorder (OCD) showed that Obsessive-Compulsive (OC) symptoms are remarkably heterogeneous, so that two patients with this diagnosis can display completely non-overlapping symptom patterns (Mataix-Cols *et al.*, 2005). This is in contrast to the current concept adopted by the DSM-IV, which defines OCD as a unitary nosological entity (American Psychiatric Association, 1994). This variability in phenotype may impact not only the findings of clinical, natural history and treatment response studies, but also complicate genetic studies and the search for vulnerability genes (Miguel *et al.*, 2005). One suggested approach to reconceptualize OCD or Obsessive-Compulsive Symptoms (OCS) is the use of OC symptom dimensions (Miguel *et al.*, 2005). OCD or OCS appears to encompass at least four consistent and temporally stable symptom dimensions (Mataix-Cols *et al.*, 2005). By considering these OC symptom dimensions as quantitative components of a more complex OC phenotype, a dimensional approach could provide a more powerful approach for the detection of genes or environmental risk factors that contribute to OC behavior (Miguel *et al.*, 2005). However, before using symptom dimensions in linkage or association analyses, it is important to examine the extent to which these symptom dimensions are heritable.

Alsobrook *et al.* (1999) were the first to use OC symptom dimensions in a family study. They reported that the relatives of OCD probands who had high scores on either the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) factors "aggressive/sexual/religious obsessions and related compulsions" or "symmetry/ordering" were twice as likely to have first-degree family members with OCD compared to individuals with low scores on these factors. Leckman *et al.* (2003) examined the familiality of OC symptom dimensions in sib pairs affected with Tourette syndrome. Significant correlations were observed between sib pairs as well as mother-child pairs for the "aggressive/sexual/religious obsessions and checking compulsions" factor, and for the "symmetry/ordering obsessions and compulsions" factor. Recently, Hasler *et al.* (2007) evaluated the familiality of different Y-BOCS dimensions within 418 sib pairs. Robust sib-sib intraclass correlations of around .2 were found for two of the four Y-BOCS factors: "hoarding obsessions and compulsions", and "aggressive/sexual/religious obsessions and checking compulsions". Smaller, but still significant, familiality was found for "contamination/cleaning", and "symmetry/ordering/arranging".

To disentangle genetic and environmental factors, twin or adoption studies are needed. No adoption studies examining OCD have been published. Twin studies of OCD have evolved from case-studies with patients with OCD to large samples of unselected subjects using the whole distribution of OC Symptoms (van Grootheest *et al.*, 2005). This last approach was first used by Clifford *et al.* (1984) who examined 419 twin pairs of monozygotic (MZ) and dizygotic (DZ) twins with the Leyton Obsessional Scale. The heritability of OCS was estimated to be 47%. The only other large study using unselected adult twins was published by Jonnal *et al.* (2000). They examined 527 female twin pairs and carried out a factor analysis on 20 Padua Inventory items. Two major factors were used in the genetic analysis, one factor which described thoughts and one which described actions, e.g. obsessions and compulsions. Heritabilities of 33% and 26% for obsessions and compulsions, respectively, were found. Recently, Van Grootheest *et al* (2007) obtained the Young Adult Self Report Obsessive-Compulsive Subscale from a group of 5893 mono- and dizygotic twins, and 1304 additional siblings and found a moderate heritability of 39% for men and 50% for women.

A next step would be to use OC symptom dimensions in an epidemiological twin sample, allowing one to investigate the genetic and environmental factors underlying different OC symptom dimensions. The (most) heritable symptom dimensions may be useful as a refined phenotype for further linkage or association studies. In this study we present multivariate analyses of the OCS data described by Jonnal *et al.* (2000). Instead of heritabilities of the classic obsession/compulsion factor model as originally reported, we present results of multivariate genetic analyses of empirically-defined symptom dimensions, giving the opportunity to investigate both the overlap and uniqueness of genetic and environmental contributions underlying OC symptom dimensions. We aim to address three major questions:

1. Can distinct dimensions within OCS be found in a general population sample of women?
2. What role do genetic and environmental factors play in the etiology of these OC symptom dimensions?
3. Are different symptom dimensions influenced by the same or by different genetic factors?

MATERIALS AND METHODS

Sample

Sample characteristics are extensively described in the publication of Jonnal *et al.* (2000). Briefly, participants in this study were from a population sample of Caucasian female twins from the Virginia Twin Registry (Kendler and Prescott, 2006). Self-report questionnaires on OC items were mailed to 1942 twins of whom 1382 returned completed questionnaires, the subjects of the current analyses. Zygosity was determined by analysis of a questionnaire and, when necessary, by DNA polymorphisms. Zygosity classifications were more than 95% accurate. The group of 1382 twins consisted of 524 complete pairs (331 MZ and 193 DZ pairs), and 334 twins whose co-twin was not assessed (175 MZ and 159 DZ twins). Their mean age was 36.6 (SD 8.4).

Scale

Twenty items of the Padua Inventory (PI) (Sanavio, 1988) were included in a self-report questionnaire. Items were chosen from all four OC dimensions of the original 60-item PI scale based on their factor loadings but also to maintain a diversity of item content. Participants were asked to respond positively or negatively to each item (yes or no) whether or not it described them. The PI is a comprehensive self-report measure for assessing symptoms of OCS. It was developed by Sanavio (1988) to obtain the most important and frequent types of obsessional complaints. From this original 60-item PI, a 41-item, the Padua Inventory Revised (PI-R) (Van Oppen *et al.*, 1995) and a 39-item version, the Padua Inventory-Washington State University Revision (PI-WSUR), have been developed by examining the factorial structure of the PI and deleting items that were poor or impure measures of these factors. The PI-R was the first study on PI items that used also data of OCD patients, instead of data of a non-clinical sample only, like Sanavio *et al.* (1988) (original 60-item version) and Burns *et al.* (39-item revision version). Both revised versions contain almost similar items, but only the PI-R is still frequently used in research. The 41 items of the PI-R form five subscales or symptom dimensions, represent symptom categories that are commonly found in OCS: Impulses (or Aggressive/Harm Obsessions), Washing (or Contamination), Checking, Rumination, and Precision (Van Oppen *et al.*, 1995; Denys *et al.*, 2004). The 20 items used in this study did not contain any Precision items. Van Oppen *et al.* (1995) reported good to excellent internal consistency for the full scale (range = .89 - .92), and the subscales (range = .66 - .89) in a group of patients with OCD, patients with other anxiety disorders, and a general population sample. OCD patients scored remarkably higher on the full PI-R and the subscales, than patients with other anxiety disorders and general population controls (Van Oppen *et al.*, 1995). Van Oppen *et al* (1995) also found that the factorial structure of the PI-R is invariant across the OCD patient group, the anxiety patient group and the general population group. In other words, they found the same factorial structure in OCD patients and general population controls.

Statistical analyses

Exploratory factor analysis was performed on the 20 items of the PI to investigate different dimensions of OC. Mplus (Muthén and Muthén, 2005) was used to perform the factor analysis with the categorical data analysis option. With this option, tetrachorical correlations are generated as basis for the factor structure. To correct for dependency of the data, we only used data from one twin, randomly chosen, per family in the factor analysis. We used an oblique rotation for the factor analysis, which allows components to correlate. We examined the scree plot and only factors with an eigenvalue of higher than 1 were retained. In accordance to Stevens (1996), factor loadings higher than .16 were regarded as significant for our sample size. Furthermore, only factors with a minimum of three items were interpreted. Instead of using factor scores, we summed the PI items with the highest loadings for the different factors. Using sum scores have the advantage that they can be easily reproduced by others and do not depend for their weights on one particular data set.
For example, when four questions scored the highest on factor 1, we summed up the answers of those four questions for every twin. The same holds for the questions which scored highest on factor two, etc. These summed scores per dimension were used for subsequent genetic analyses. Internal consistency of each dimension was evaluated using Cronbach's alpha.

Genetic and environmental influence on the OC symptom dimensions were estimated using structural equation modeling. The influence of the relative contributions of genetic and environmental factors on individual differences in OC symptoms can be inferred from the different levels of genetic relatedness of MZ and DZ twins. Variance in OC symptom scores may be due to additive genetic effects (A), shared environmental effects (C), and nonshared environmental (E) effects. Because MZ twins share all their segregating genes, the genetic effects are perfectly correlated in MZ twins. DZ twins correlate .5, because DZ twins share on average half of their segregating genes. Shared environmental effects, environmental experiences that make twins from a pair similar in their liability to OC symptoms, correlate 1.0 within both MZ and DZ twins. Nonshared environmental effects are, by definition, uncorrelated in both MZ and DZ twin pairs and include both the effect of individual experiences and measurement error. Because the distributions of the OC symptom dimensions were non-normally divided, characterized by skewness, i.e., many respondents scored zero, we used categorical data analysis within Mx (Neale *et al.*, 2003). In this approach, a liability threshold model is applied to the ordinal scores, using a threshold to define affection status. It is assumed that a person is "unaffected" if his or her liability is below this threshold or "affected" if above this threshold. In the present study, a cutoff score of one was used to gain roughly two groups of the same size. This means that a person is "unaffected" for a symptom dimension if they possessed a score of zero on this symptom dimension or "affected" with a score of one or higher.

After fitting a fully saturated model, a model with all correlations and thresholds estimated freely, we fitted both independent and common pathway multivariate models to investigate the pattern of covariation among the OC dimensions and their relation to the construct OC behavior. The independent pathway model specifies common factors of A, C and E loadings on all the outcome measures (e.g., OC dimensions). Besides these common factors, it allows separate A, C and E decompositions of each observed OC dimension. To investigate whether the OC dimensions define a single construct of OC behavior, a common pathway model was also fit. In this model, both genes and environment are assumed to contribute to one latent (unmeasured) variable (e.g., OC behavior) which is responsible for the observed covariation between the scales. Genetic and environmental factors specific to each OC dimension are also incorporated in the model. When fitting models to ordinal data using a threshold approach, a constraint on the total latent variance is needed. For the independent pathway model, we constrained the total variance for each of the three dimensions to equal 1. For the common pathway model also the variance of the latent common phenotype was constrained to be 1. For more detailed information about independent and common pathway models see Martin and Eaves (1977), and Kendler *et al.* (1987).

We tested whether a model could be simplified by dropping one or more latent factors. The non-shared environmental factor was never dropped from the model, because, in addition to non-shared environmental experiences, this factor includes measurement error. The models were fitted to raw data with Mx (Neale *et al.*, 2003) by the method of maximum likelihood estimation. This allowed the use of all twin data, including those without an interviewed co-twin. Goodness-of-fit was assessed by likelihood-ratio chi-square (X^2) tests. These tests compare the differences between two times the log likelihood of a full model and a restricted nested model. This difference is distributed as X^2, and the degrees of freedom (df) for this test are equal to the difference between the number of estimated parameters in the full model and that in the restricted model. More technical details of genetic model-fitting analyses are reviewed elsewhere (Neale and Cardon, 1992).

RESULTS

Factor analysis

The results of the factor analysis using the 20 PI items were unclear and showed a difficult to interpret five-factor solution. We then decided to include only those Padua Inventory items which were used in the 41-item PI-R (Van Oppen *et al.*, 1995). Of the 20 items we collected, 17 met this criterion. Interestingly, the factor analysis of these 17 items showed an interpretable four-factor solution, which explained 46.6% of the variance (table I). Inspection of the items included in these factors suggested that the components represented (1) Rumination, (2) Contamination, (3) Impulses or Aggressive/Harm Obsessions, and (4) Checking. The internal consistency of each factor was .67, .62, .48, and, .64 respectively. The factor Impulses clearly showed a lower internal consistency. Further inspection of this factor revealed that more than 90% of the participants scored 0 on this symptom dimension, which caused very low variation within this factor. We decided not to include this factor in our genetic analyses. Table II shows the phenotypic correlations between the dimensions Rumination, Contamination, and Checking.

Genetic analyses

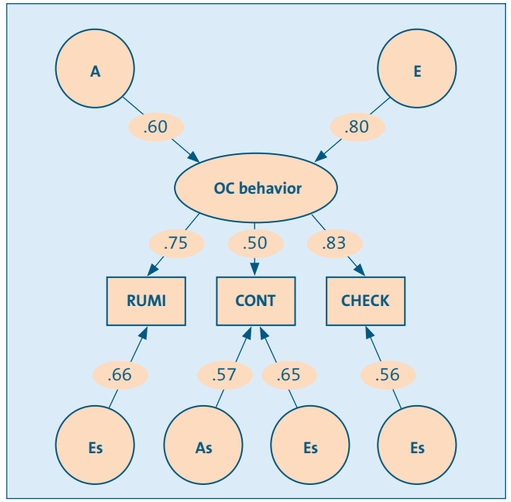
Tetrachoric twin correlations, both within dimensions and across dimensions, are seen for both zygosity groups in table III. For all dimensions, MZ correlations were higher than DZ correlations, indicating the influence of genetic factors on OC dimensions (diagonal). However, for the factor Checking, shared environmental factors also seem important, because the MZ correlation is less than twice the DZ correlation. The cross-dimension twin correlations (off-diagonal), i.e. the correlation between a OC dimension of the first-born twin with a different OC dimension of the second-born twin and vice-versa, give insight into the role of genes and environment in explaining the sources of the correlation between dimensions. Here we also see that MZ cross-dimension correlations are larger than DZ

Table 1. Results of factor analysis of 17 Padua Inventory items used in present study

	Factor			
	Rumination	Contamination	Impulses	Checking
Are you the type of person:				
Who after doing something carefully, still has the impression it is either done badly or is not finished?	**1.000**[a]	.083	-. 246	-.111
Who has to do things several times before thinking they are done properly?	**.687**	.107	-.101	.203
Who imagines that catastrophic consequences may result from absent-mindedness or minor errors you have made?	**.648**	-.069	-.013	.150
Who invents doubts and problems about most of the things you do?	**.562**	-.148	.231	.089
Who has unpleasant thoughts that come into your mind against your will, and which you cannot get rid of?	**.372**	-.066	.305	.231
Who finds it difficult to touch garbage or dirty things?	.083	**.850**	.087	-234
Who finds it difficult to touch an object which has been touched by strangers or certain people?	-.007	**.750**	-.047	.184
Who has to wash their hands more often and longer than necessary?	-.030	**.689**	.038	.173
Who avoids using public toilets because of fear of disease and contamination?	-.025	**.582**	-.015	.373
Who sometimes has to wash or clean yourself because you think you may be dirty or "contaminated"?	.108	**.474**	.043	.341
Who when looking down from a bridge or very high window, feel an impulse to throw yourself into space?	-.240	-.210	**.964**	.341
Who when a train approaches, sometimes thinks of throwing yourself under the wheel	-.156	.238	**.940**	-.259
Who, while driving, sometimes feels an impulse to drive the car into someone or something?	.110	.063	**.795**	-.104
Who sometimes feels a need to break or damage things for no reason?	.308	.061	**.438**	.-.066
Who checks and rechecks gas burners, water faucets, and light switches after turning them off?	.054	.050	-.003	**.799**
Who has to return home to check doors, windows, and drawers etc., to make sure they are properly shut?	-.027	.182	.009	**.761**
Who has to keep on checking forms, documents, checks etc. in detail to make sure they have been filled out correctly?	.220	.046	-.064	**.695**

[a]The numbers represent the factor loadings on the four factors and bold numbers are the primary loadings on that factor.

Figure 1. Path diagram of the final Common Pathway Model



Rumi, rumination; Cont, contamination; Check, checking; A, additive genetic; C, shared environment; E, nonshared environment; As, specific additive genetic; Cs, specific shared environment; Es, specific nonshared environment; OC behavior, latent phenotype. The numbers reflect path coefficients. The square of the path coefficients is the proportion of explained variance. The total variance of the latent phenotype (OC behavior) and observed variables (Rumination, Contamination, and Checking) is constrained to be 1 (i.e., four constraints). For example, variance of Rumination is .66x.66 (=.44) + .75x.75 (=.56) = 1.

cross-dimension correlations. This suggests that genetics may help explain the overlap between the different dimensions. However, for the dimensions Rumination and Checking, shared environmental factors also are important, given that the MZ correlation is only slightly larger than the DZ correlation.

In the saturated model, we were able to constrain the thresholds for all three factors to be equal in both twins from a pair, and in both MZ and DZ pairs ($\chi^2(9) = 13.2$, $p = .16$). Compared with the multivariate fully saturated model (table IV), the independent pathway fitted well to the data ($\chi^2(24) = 34.4$, $p = .08$). The common pathway model structure is different from that of the independent pathway model (it introduces a latent variable) and can be formally tested as a nested sub-model. Comparing the fit of the common pathway model to the independent pathway model produced a non-significant chi-square test ($\chi^2(4) = 6.0$, $p = .20$). This indicates that the more restrictive common pathway model provides a more parsimonious explanation than does the independent pathway model. The common pathway model is therefore the model of choice. Figure I displays the common pathway model with the estimates of the structural parameters. The total variance of the latent phenotype (OC behavior) and observed variables (Rumination, Contamination, and Checking) is constrained to be 1. The proportions, the square of the parameters of figure I, of genetic and environmental influences from the best fitting common pathway model are given in table V.

For the latent OC behavior construct, 36% of its variance was attributed to genetic factors (A) and the rest of the variance was explained by nonshared environmental factors (E). Shared environmental factors (C) could be dropped without any loss of fit, which means that the influence of shared environmental factors is zero on the latent OC construct, and this factor is not shown in figure I. For clarity, a CE model also fitted the data ($\chi^2(1) = 1.4$, $p = .23$), though worse than the AE model. Dropping both A and C resulted in a significantly worse fit ($\chi^2(2) = 13.5$, $p = .001$). The latent OC behavior phenotype explained more than half of the variation of Rumination (56%) and Checking (69%), but interestingly only 25% of Contamination. So 75% of the variation of the Contamination dimension is explained by specific factors, with 33% explained by genetic factors and 42% by nonshared environmental factors. The shared environmental factor explained 0% of the variance and could be dropped without any worsening of the fit and is therefore not shown in figure I. For both the Rumination and Checking dimensions, genetic and shared environmental specific factors could be dropped without a significant decline in fit ($X^2(2) = .53$, $p = .77$, and $X^2(2) = 2.42$, $p = .30$, respectively), meaning that specific familial factors do not play a role in these two OC dimensions.

Table 2. Pairwise correlations (within person) between OC dimensions

	Rumination	Contamination	Checking
Rumination	1.00		
Contamination	.30*	1.00	
Checking	.57*	.37*	1.00

* p < .01

Table 3. Twin correlations per OC dimension

		Twin 1		
	Factor	**Rumination**	**Contamination**	**Checking**
Twin 2	**Rumination**	.25/.11	-.21	.20
	Contamination	.12	.42/.05	.05
	Checking	.23	.15	.35/.28

Correlations for MZ twins and DZ twins are reported below and above diagonal respectively. On diagonal, correlations for MZ twins are reported on the left and for DZ twins on the right.

DISCUSSION

This is the first twin study to investigate genetic and environmental effects on different dimensions within OC symptoms in a population-based sample. We first completed a factor analysis on 17 PI-R items to search for distinguishable OC dimensions. We then completed multivariate twin analyses of three OC dimensions. Three main conclusions can be drawn. First, using the items of the PI-R of a population based sample of female twins in a factor analysis, four OC dimensions could be identified: Rumination, Contamination, Checking and Impulses. Second, using three of the four dimensions in the genetic analyses the common factor model best fitted the data, which means that there is a common OC behavior phenotype explaining variance of all three dimensions, and this phenotype is influenced by genes and nonshared environment. Third, besides genes for the broad OC behavior phenotype, specific genetic influences are also seen for Contamination dimension, explaining a fair amount of its variation.

Table 4. Model fitting results for heritability of YASR-OC dimensions

Number of model	Type of model[a]	-2LL	χ^2	df	p	parameters	Compared with model
1	Fully saturated model	4683.0	-	-	-	42	-
2	Full Independent pathway model	4717.4	34.4	24	.08	18	1
3	Full Common pathway model	4723.4	6.0	4	.20	14	2
4	**Common pathway model with common AE**	**4723.4**	**0**	**1**	**1.00**	**13**	**3**
5	Common pathway model with common CE	4724.8	1.4	1	.23	13	3
6	Common pathway model with common E	4738.3	13.5	2	.001	12	3

[a] A=additive genetic effects; C=common or shared environmental effects; E= nonshared or individual-specific effects.

Table 5. Proportions of variance explained by genes and environment from best fitting common pathway model

Latent phenotype			Common pathways[a]		Specific pathways[b]		
	A	E			A	C	E
OC behavior	.36	.64	Rumination	.56	.-	-	.44
			Contamination	.25	.33	-	.42
			Checking	.69	-	-	.31

A = genetic influences; C = shared environmental influences; E = nonshared environmental influences
[a] Variation shared by the latent phenotype (OC behavior) and the specific factors (OC dimensions). Proportions of common pathway and specific pathways add up to 1 for each factor.
[b] OC factor or Dimension Specific Contributions

The factor structure of the PI items we found was similar to that found in earlier studies using PI items within OCD patients (Van Oppen *et al.*, 1995; Denys *et al.*, 2004) and general population samples (Van Oppen *et al.*, 1995, Burns *et al*, 1996). We could not identify the dimension related to precision because no corresponding items were included in this study.

The results of this multivariate analyses show the extent to which symptom dimensions that cluster share a common genetic basis. The common factor model fitted the data the best. The common factor, i.e., OC behavior phenotype, was influenced by both genetic and nonshared environmental influences. Twin studies of OCD in adults so far also found no evidence for shared environment (Van Grootheest *et al.*, 2005). Our results further indicate that, in addition to a common factor, sharing genes related to three dimensions, only the contamination dimension may possess also specific genetic factors, while for the other two dimensions we have to conclude that specific familial influences are not of importance. Interestingly, the Contamination dimension is also the dimension of which only a quarter of the variation is explained by the common OC behavior phenotype. This means that the Contamination dimension is a relative independent dimension.

These results support the findings of some of the family studies investigating the familiality of OC symptom dimensions, based on Y-BOCS items (Leckman *et al.*, 2003; Hasler *et al.*, 2007). Hasler *et al.* (2007) found significant sib-sib correlations for Checking compulsions and the Contamination/Cleaning dimension. These two Y-BOCS dimensions are comparable with the PI-R Checking and Contamination dimensions we found. However, we found no familial effects for the Checking dimension, but the study of Hasler *et al.* (2007) did not account for the possibility of common versus specific familial effects.

These results suggest that, in spite of clinical heterogeneity, a broad OC behavior phenotype exists, influenced by both genes and nonshared environment. This corresponds well with clinical presentations of OCD: OCD patients typically score positive on a wide variety of symptoms from multiple dimensions, with usually one or two dimensions appearing more prominent (Leckman *et al.*, 1997). Our results seem also in line with Mathews *et al.* (2004) who examined the structure of OC symptoms in a non-clinical population and concluded that this broad OC behavior phenotype, they call it "obsessionality", is phenomenologically similar to OCD and is likely to comprise a continuum with OCD. This may implicate that, besides a traditional categorical model of OCD, an underlying quantitative OC behavior phenotype could be used to provide an alternative strategy for the detection of genetic susceptibility loci that contribute to OCS or OCD (Miguel *et al.*, 2005).

Another approach would be the use of the contamination dimension, showing clear specific genetic influences explaining a substantial amount of its variance.

These results should be interpreted in the context of four limitations. First, we only selected a subset of items from the PI which probably increased total error variance. Error variance cannot be distinguished from nonshared or individual-specific environment, and therefore it is likely that the impact of genetic influence on the etiology of OCS is underestimated. Second, the present study only included women, so results cannot be assumed to hold equally for males, although Van Grootheest *et al.* (2007) recently found in a large twin-family study, that the same genetic risk factors were expressed in men and women for OC behavior. Third, because of the use of a threshold model (Derks *et al.*, 2004), and the fact that number of MZ twins exceeded the number of DZ twins (Posthuma and Boomsma, 2000), the power to distinguish genetic influences from shared environmental influences was moderate. Fourth, the findings of this analysis are predicated on the assumptions of the method used. These assumptions include no large degree of assortative mating and the validity of the equal environment assumption (EEA). The EEA states that environmental influences are shared to the same extent by MZ and DZ twins. Maes *et al.* (1998) found that significant but moderate primary assortment exists for psychiatric disorders. However, it was concluded that the bias in twin studies caused by the small amount of assortment is negligible. Jonnal *et al.* (2000) tested the EEA for OC symptoms in the current sample and concluded that the EEA was not violated.

The limitations of the present study give direction for future twin studies investigating OC dimensions. First step is to replicate our results in a large twin sample with an adequate MZ/DZ twin ratio to overcome power limitations (Posthuma and Boomsma, 2000). Second, assessing OC symptoms in both male and female twins allows one to test for sex-differences within symptom dimensions. Finally, it is preferable to assess OC symptoms with the complete PI-R and/or Y-BOCS (Goodman *et al.*, 1989). The relatively new self-report version of the Dimensional Y-BOCS (DY-BOCS) (Rosario-Campos *et al.*, 2006), especially developed to assess OC dimensions, seems promising in this respect. Using both the (D)Y-BOCS and PI-R has the advantage of assessing unique factors: Rumination is represented solely in the PI-R and "somatic/religious/sexual obsessions" and "hoarding obsessions/compulsions" solely in the (D)Y-BOCS.

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CHAPTER 12

Discussion & Summary

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Discussion & Summary

This thesis describes the study of genetic and environmental influences on individual differences in Obsessive-Compulsive Symptoms (OCS) across a large part of the lifespan. In this last chapter, the findings that have resulted from this project are summarised, discussed and some directions for future studies are considered.

PART I. INTRODUCTION TO OCD, OCS AND TWIN STUDIES

Chapter 2 provided a brief overview of Obsessive-Compulsive Disorder (OCD). OCD is a complex psychiatric disorder characterized by obsessions and/or compulsions. Obsessive-compulsive disorder has a relatively high prevalence of roughly 1% and is a highly disabling disease. The disorder is associated with shame, which causes long delays in accessing treatment. Differences between people in the liability to develop OCD are caused by a combination of genetic and environmental factors. Effective treatments exist, either pharmacotherapy or cognitive behavior therapy. In **chapter 3**, all known published twin studies on OCD/OCS have been described and over 70 years of twin research of OCD/OCS was presented. Four different approaches to twin studies of OCD/OCS were recognized. These approaches include (1) case-studies of twins with OCD from the old literature, (2) twin studies of OCD using *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria, (3) twin studies of OCD using a dimensional approach, comparing resemblances in monozygotic and dizygotic twins, and (4) twin studies of OCD using a dimensional approach, analyzing the data with Structural Equation Modeling. It was concluded that only the studies using the last method have convincingly shown that obsessive-compulsive symptoms are heritable with genetic influences in children in the range of 45% to 65%. In adults, studies are suggestive for a genetic influence on obsessive-compulsive symptoms, ranging from 27% to 47%, but a large twin study using a biometrical approach with continuous data is still needed to provide conclusive evidence, including a closer look at sex-differences, issues of phenotypic assortment and cultural transmission in genetic architectures. That is exactly what I have done in this thesis.

PART II. HERITABILITY, ASSORTATIVE MATING AND CULTURAL TRANSMISSION OF OCS

In **chapter 4** the genetic and environmental influences on OC symptoms were investigated in a large population based twin-family study. The OC scale of the YASR, based on the CBCL-OCS, developed by the group of Hudziak (Nelson *et al.*, 2001; Hudziak *et al.*, 2006) was used. The YASR-OCS contains the same 8 items as the CBCL-OCS, except that items are worded in the first person. At the best cut-off point of 7, the sensitivity and specificity of the YASR-OCS was 82.4% and 69.7% respectively, when compared to clinical controls, with a Cronbach's α coefficient of .69. YASR-OCS data were available in 5893 mono -and dizygotic twins, and 1304 additional siblings. There was no evidence for a special twin environment as familial resemblance was the same for DZ twins and non-twin siblings. The same genetic risk factors for OC behavior were expressed in men and women. Depending on the choice of fit-index we found small (heritability of 39% for men and 50% for women) or no sex-differences (heritability of 47% for both men and women) in heritability. The remaining variance in OC liability was due to non-shared environment. Thus, in the largest study to date, we found that OC symptoms showed a moderate heritability with no qualitative and, at most, small quantitative differences in genetic architecture.

The **fifth chapter** explored the existence and causes of marital resemblance for obsessive-compulsive, anxious and depressive symptoms in a population-based sample of around 1400 twin-spouse and over 850 parent pairs. Resemblance between spouses can be due to phenotypic assortment, social homogamy or marital interaction. Phenotypic assortment means that partner selection is based directly on the partner's phenotype; there is a preference for a phenotype like one's own, resulting in marital resemblance. Social homogamy refers to the tendency for individuals to have partners with similar social background, e.g. coming from the same religious background. Under social homogamy partner selection takes place within social strata, which are correlated with the phenotype under study. Marital interaction or shared influences after marriage refers to a process of mutual influences between spouses living together. In addition to the process of initial assortment, spouses may become more similar the longer they are married due to mutual influence between spouses or by sharing the same pathological factors. A significant degree of assortment, if it is due to phenotypic assortment, has consequences for the genetic architecture of a population. We found small but significant within-trait correlations between .1 and .2 for spouse similarity in obsessive, anxious and depressive behavior as measured by the YASR-OCS, YASR anxious-depressed subscale and the STAI. Cross-trait correlations were also significant but lower. There was no correlation between length of relationship and marital resemblance, indicating that resemblance between spouses does not increase as a function of duration of marriage. Marital correlations were small, which makes it difficult to distinguish between social homogamy and phenotypic assortment, but as shared environmental influences explaining individual differences in OC symptoms have hardly been found in adults, it seems likely that phenotypic assortment is the main process. It is unlikely that correlations of this size will have a large impact on genetic studies. The purpose of **chapter 6** was to examine the role of genetic and environmental factors to variation in OC symptoms using an extended twin design, including 4408 twins, 1309 siblings, and 2305 parents. This design allows us to test for genetic and environmental factors, while taking phenotypic assortment and cultural transmission, the influence of the parental phenotype on shared environmental factors of the children, into account. The 12-item Padua Inventory Revised Abbreviated was used to measure OC symptoms. We found that both additive genetic and non-shared environmental factors contributed significantly to the variance of OC symptoms in men and women. In males, shared environmental influences played a relative large role (27%) with a small role for genetic factors (1%). Significant influence of cultural transmission was only found for men, but was minimal (<1%). Non-shared factors explained 71% of the variance of OC symptoms. For women, the heritability was estimated at 37% and non-shared environment explained 63% of the total variance in individual differences in OC symptoms. No evidence for a special twin environment was seen, cultural transmission, from parent to son, was small, suggesting that the effect of the shared environment in men mainly has a non-parental origin and is primarily due to within generational influences.

We concluded from part I that a large twin study on OC symptoms was lacking. Part II fills up this gap with two large twin studies using two different OC questionnaires. One may conclude that OC symptoms are heritable in women, independent of the measurement instrument , with roughly a heritability of 40-45%. For men, we found an similar heritability using the YASR-OCS, but also an influence of shared environment when OC was assessed with the Padua-ABBR. The results of the YASR-OCS for both men and women are in line with the results found in children and adolescents, so it seems that the shared environmental influences found for the Padua-ABBR are the exception. The Padua showed also low heritabilities in the Jonnal *et al.* study (2000) and has low correlations with for example the YBOCS (Denys *et al.*, 2004). The largest differences between YASR-OC and Padua-OC were seen for the DZM-correlations, which are quite high for Padua-OC in comparison with the DZM-correlations in the YASR-OCS study. The MZM correlations of the Padua-ABBR are in the same range as in the YASR-OCS study (chapter 4). Future research must establish whether the shared influences in men for the Padua-ABBR is a coincidental finding or that it was "real" shared environment (C). Earlier, C had not been detected in twin studies of OC symptoms, except in children at the age of 12 years (chapter 7). Furthermore, when YASR-OCS and Padua-ABBR data were used together in longitudinal analyses, no significant shared environmental factors were found (chapter 9).

Another focus of Part I was testing of several assumptions of twin studies like the absence of assortative mating or gene-environment correlation induced by simultaneous cultural and genetic transmission. Assortative mating exists for OC symptoms, but it is small, so that the bias in estimates for A, C and E is minimal. Gene-environmental correlations induced by genetic and cultural transmission were significant only for men, but explained only a small part of the variation in OC symptoms. Consistent with earlier findings (e.g. Jonnal *et al.*, 2000) no evidence was found for a special twin-environment (chapters four and five).

One assumption which was not tested in this thesis is whether OCD reflects the extreme of a normal distribution, while OC symptoms represent a milder form of the latter. There is indirect evidence that this is the case, but it is not explicitly tested yet, for example by fitting item-response models, as van den Oord *et al.* (2003) did for depression. The indirect evidence lies in the fact that family studies (Pauls *et al.*, 1995, Nestadt *et al.*, 2000) show that family members of OC patients have fewer OC symptoms than the proband with OCD, but more than controls and their families. However, without directly proving this assumption, one should be careful with conclusions that extend findings in the general population to a specific disease.

Part II of this thesis (Heritability, assortative mating and cultural transmission of OCS) has important clinical consequences. It is not long ago that parents of patients with psychiatric disorders, such as schizophrenia, were blamed for the disease of their offspring. Twin studies can be particularly effective in disentangling myths from facts, thus providing a tool for health care workers to inform patients and their families on the etiology of the disease, which often is mainly caused by genetic factors and individual experiences, instead of adverse family environment. Thus our research on OC symptoms might provide an opportunity to relieve

the feelings of guilt and shame that patients and their families meet.

The results from *part II* have enabled us to answer some advanced genetic epidemiological questions, with respect to sex differences in genetic architecture of OC symptoms, and influences of phenotypic assortment, marital interaction, cultural transmission and social homogamy. However, several questions need to be addressed in future research. As OCD is not a discrete diagnostic entity with sharp external boundaries (Denys, 2004), potential research questions include: Are the genetic risk factors specific to OC symptoms or shared with other psychiatric disorders? To what extent are the effects of these genetic risk factors mediated through intermediate phenotypes such as personality or neuropsychological processes? Do genetic risk factors moderate the effect of environmental risk factors on disease liability, e.g., genetic control of sensitivity to the environment? Are these moderating effects of genes on specific environmental risk factors conditional on age? And if so, what are specific age periods that make persons particularly vulnerable for gene x environment interaction? How can environmental and genetic risk factors be better characterized? We hope to answer some of these questions in the following years using data of the Netherlands Twin Register.

PART III. GENETIC AND ENVIRONMENTAL INFLUENCES ON OCS OVER TIME

The objective of **chapter 7** was to assess genetic and environmental contributions underlying stability in childhood obsessive-compulsive symptoms. The use of both maternal and paternal ratings is unique. An advantage of a design in which multiple raters assess the behavior of genetically related subjects (i.e., twins) is that a distinction can be made between variance that is explained by a common perception of the parents (i.e., common phenotype) and variance that is explained by a unique perception of each parent on the behavior of their child (i.e. unique or rater specific phenotype). The common perception is not confounded by rater bias or measurement error (Hewitt *et al.*, 1992). The unique phenotype leaves room for specific views of a certain rater, but may include both rater bias and measurement error.

Maternal and paternal ratings on the 8-item Obsessive Compulsive Scale of the Child Behavior Checklist (CBCL-OCS) in Dutch mono- and dizygotic twin pairs from 8083 families were collected longitudinally, at ages 7, 10, and 12 years.

OC behavior assessed by the CBCL-OCS showed a moderate stability with phenotypic correlations of around .50 for boys and for girls. Stability of OC behavior was influenced mainly by genetic factors, but environmental factors shared by children growing up in the same family and by non-shared environmental factors also played a substantial role. Stability for OCS was lower when data were analyzed using cut-points, than when quantitative definitions were used.

Chapter 8 described a cross-sectional study of genetic and environmental contributions to self-report obsessive-compulsive symptoms, the 8-item Obsessive-Compulsive Scale of the Youth Self Report (YSR-OCS), in Dutch adolescents at ages 12, 14, and 16 years. At age 12 no difference in prevalence was found for OC symptoms in boys and girls. At age 14 and 16, the prevalence was higher in girls. At all ages, genetic factors contributed significantly to OCS variation; 27% at age 12, 57% at age 14 and 54% at age 16. There were no sex-differences in heritability. Only at the age of 12, environmental factors shared by children from the same family explained part (16%) of the individual differences in OC symptom scores. At ages 14 and 16 years no contribution was observed of shared environment.

Chapter 9 presented the first estimates of genetic and environmental contributions underlying stability in adult obsessive-compulsive behavior. The YASR-OCS was obtained from a group of mono -and dizygotic twins in 1991, 1995 and 1997 and the Padua Inventory Revised Abbreviated (PI-R ABBR) in 2002 with a mean age in 1991 of roughly 18 years till a mean age of 33 in 2002. Stability over time of obsessive-compulsive (OC) symptoms was examined and analyzed as a function of genetic and environmental components.

Heritability of OC behavior was around 40% at each time-point, independent of the instrument used. OC behavior was moderately stable with correlations between .39 and .61 for subsequent time-points. Variance in stability of OC behavior is influenced for 70% by additive genetic factors. Genetic correlations over time of roughly .8 were found for both men and women between the first three time-points with somewhat lower correlations of .6 between the first three time-points and the last time-point. Although the PI-R ABBR introduced new genetic influence, it seems in general that the same genes play a role in OC behavior over time. This implies that OC data of different ages can be pooled together in gene-finding studies.

Part III has focused on heritability of OC symptoms over time and underscored the justification of a lifetime approach to behavior and disease. The same 8 items regarding OC behavior were assessed in children, adolescents and adults. The longitudinal study in children simultaneously analysed ratings of OC symptoms of both fathers and mothers, trying to get a reliable measure. The study clearly shows that genetic factors are indeed important in stability of OC symptoms, but that shared and non-shared environmental factors also play a role. This mix of factors is absent in adults, for whom we found that genetic factors explain the majority of the covariance of OC symptoms between time-points. The longitudinal study of OC symptoms in adults has used a simplex model, which can disentangle stable genetic factors from new genetic factors. In general, stable genetic influences seem to be responsible for the stability of OC symptoms. Interestingly, for stability in children, environmental factors are more important than in adults. This may indicate that how earlier treatment starts, the better environmental factors can be influenced.

The study in adolescents showed three cross-sectional analyses at three different ages in adolescence. The finding of shared environmental at the age of 12 is striking, as it is found independent of the rater, in this case mother, father and self reports. However, in general we found stable heritabilities of around 55% from childhood to adolescence, with only a small decline to roughly 45% in adults. Stability in OC symptoms in children is caused by the same genes over time. This seems also the case for adults. We do not yet know if the genetic factors that are expressed in children are the same as in adults. Therefore, the results of this part of the thesis raise important questions. For example: what is the stability of OC behavior in adolescence and are the genetic factors the same over time in adolescence? Are the genes responsible for OC symptoms in childhood the same as in adolescence, or even in adulthood? As the children are growing older and the sample is growing larger, we hope to publish longitudinal research on OC symptoms from childhood till adulthood, to solve these questions.

The longitudinal study in adults, using two different questionnaires to detect OC symptoms, raises the question if these two measurements measure the same trait, as genetic innovations were seen for the PI-R ABBR. The items of the YASR-OCS measure the existence of OC symptoms in general, while the PI-R ABBR measures more specific OC symptoms. Interestingly, this study also puts the findings of shared environment in men in chapter 6 in perspective. In this study we not only model the cross-sectional covariance between twins, but also the cross-twin cross-time correlations. Note that the same data (without the parents) were used for time-point 2002 as in chapter 6. Used in a longitudinal design with different OC questionnaires, shared environment could easily be dropped. As a consequence, the estimation of genetic factors in men is quite higher than in chapter 6.

The longitudinal study in adults also emphasizes the need to use more measurements at once, to capture all the information and not missing important aspects of the phenotype. It is notable that the well-known clinician administered Y-BOCS (Goodman *et al.*, 1989) and the self report PI-(R) (Sanavio, 1988; Van Oppen *et al.*, 1995) contain different symptom dimensions and have a correlation of only .27 (Denys *et al.*, 2004). This means that in clinical practice it is recommended to use both questionnaires to capture the entire spectrum of symptoms. For research, the ideal situation within the large scale of twin studies would be to have a relative compact self report scale, still capturing all the information, including the several important symptom dimensions within OCD. It would be worthwhile to have an internationally accepted short screener, developed in such a way that the scale is normally distributed, preventing statistical complications. The recently developed DY-BOCS (Rosario-Campos *et al.*, 2006) is too long and time consuming to use in a large-scale epidemiological studies. The 18-item OCI-R (Foa *et al.*, 2002) is promising with a recent study indicate that the subscales of the OCI-R are valid measures of symptom dimensions of OCD (Huppert *et al.*, 2007).

PART IV. ENVIRONMENTAL FACTORS AND SYMPTOM DIMENSIONS IN OCS

Chapter 10 focused on environmental factors that protect or exacerbate obsessive-compulsive behavior using a special twin design of discordant and concordant monozygotic twins. Since the PI-R ABBR was used to select the MZ pairs for the study, the use of the Padua Inventory Revised ABBR was evaluated. To investigate whether the PI-R ABBR can accurately screen for OCD, and to establish cut-points of OC behavior, Receiver Operating Characteristic (ROC) analyses were carried out. At the best cut point of 16, the sensitivity was .74 with a specificity of .72, when compared to clinical controls. Cronbachs' α of the scale was .73. From the 2002 wave of data collection in the NTR, we selected 25 monozygotic (MZ) twin pairs who were discordant (high-low) on the PI-R ABBR, 17 MZ twin pairs concordant high and 34 MZ pairs concordant low. Within-discordant MZ pair comparisons were used to investigate environmental factors unique to the individual, whereas between-concordant pair comparisons were used to study environmental factors shared by both twins of a pair.

The high scoring MZ twins of the discordant group reported more life events, especially sexual abuse, than lower scoring twins. The between-pair comparisons showed lower birth weight in the discordant MZ pairs than in the concordant MZ pairs. The discordant pairs revealed lowest birth weight compared to the concordant pairs. Further, the concordant high scoring twins tended to report in fewer instances to have a religious background, and tended to be less active in church. Finally, the concordant high scoring twins as well as their

partners and fathers had the lowest educational level when compared to the other groups. Longitudinal data on OC symptoms, anxiety and depressive symptoms in the concordant and discordant groups revealed an earlier age at onset of OC and related symptoms in the concordant high group (from 1991 on) than in the discordant group (mostly from 1997 on), confirming previous reports of an association of early-onset OC symptoms with higher genetic load. Parent scores of OC symptoms and anxious-depression suggested intermediate genetic load in the discordant group.

Chapter 11 described the first attempt to estimate a heritability of obsessive-compulsive symptom dimensions. As recent research has shown that Obsessive-Compulsive Symptoms differ remarkably between patients and can be divided into several symptom dimensions, the objective was to examine to what extent these symptom dimensions are heritable. We studied a population sample of 1383 female twins from the Virginia Twin Registry. OCS was measured by a questionnaire with 20 items from the Padua Inventory. After factor analysis, three reliable OC symptom dimensions were retained: Rumination, Contamination, and Checking. These OC dimensions were analyzed with multivariate genetic models to investigate both the overlap and uniqueness of genetic and environmental contributions underlying OC symptom dimensions.

The multivariate common pathway model provided the best description of the data. All symptom dimensions share variation with a latent common factor, i.e., OC behavior. Variation in this common factor was explained by both genes (36%) and environmental factors (64%). Only the Contamination dimension was influenced by specific genes and seemed to be a relatively independent dimension. The results suggest that a broad OC behavioral phenotype exists, influenced by both genes and non-shared environment. In addition, we found evidence for specific genetic and environmental factors underlying the Contamination dimension.

In *Part IV* we focused both on the environmental factors which play a role in Obsessive Compulsive symptoms and on symptom dimensions within OC symptoms.

The discordant MZ twin design is intriguing. Why is there a difference in a trait, while we know that the genome sequence is in general the same within a MZ twin pair? That this last conclusion is not always the case proves a recent publication of Bruder *et al.* (2008). They found clear differences in copy-number variation (CNV) between monozygotic twins, indicating that subtle differences exist between the genome of MZ twins. However, in general the discordant MZ twin design, with variants like comparing high-scoring and low-scoring twins, is especially suitable to unravel environmental causes to symptoms or diseases for example by changing gene-expression. We found a general risk factor like sexual abuse, but also a possible protective factor like a higher level of education. In addition to the small sample size, we were confronted in this study with a major problem which many studies face: How does one measure environmental factors in a precise and reliable manner? Although genetic factors play a role in many disorders and traits, the role of environmental factors and, more specifically, the interaction between both is in many cases at least as important. I predict that we will refocus on environment in the next decade, following large groups over time, while precisely registering environment, for example by computerized diaries. This type of research in combination with genetic data like for example gene expression profiles could give us further clues in unravelling the causes of OCS/OCD. At this moment, there is paucity within the OCD literature of statistical sound studies of environmental factors in OC phenomenology.

In addition to the study of chapter ten, we recently conducted an fMRI study with a subgroup of the MZ twin pairs discordant for OC symptoms described in chapter ten (den Braber *et al.*, 2008). Using a Tower of London planning paradigm twins with OCS showed significantly decreased brain activation during planning in dorsolateral prefrontal cortex, thalamus pulvinar, and inferior parietal cortex. These findings are consistent with the hypothesis of disturbed cortico-striato-thalamo-cortical (CSTC) circuitry underlying OCS and show the power and possibilities of the discordant twin design.

The study in collaboration with the group of Kendler focused on the fact that OCD is a heterogeneous disease with many faces. A general obsessionality factor exists influenced by genetic and environmental factors. However, besides a general factor there is evidence for specific genes and environment for the contamination dimension. Speculating on these results, it would imply that common genes and environment will make you obsessed, but that specific genes and environment determine which kind of symptoms you will have. The results are intriguing, but, more research is needed. In an ideal situation, data of a large group of male and female twins, who filled in two complete OC symptom measurements (for example a self report version of the Y-BOCS and the Padua Inventory), would be analysed in the same manner as described in our study to answer questions like: Which dimensions have specific genes and environment? Are there any sex differences? Is there any difference in heritabilities of specific symptom dimensions? When we are able to follow this group of twins in a longitudinal way, we also can answer questions like: Are dimensions stable over time? Are there sex-differences in stability? Is stability caused by genes or environment?

Part IV showed two studies with different approaches: a categorical one and a more continuous approach. Each approach has its merits and both show additional value, although within the psychiatric discipline, research, especially in the clinical field, seems to stick to category-based DSM-IV approaches. It would be a good step forward if researchers also underscore the value of the more continuous approaches and facilitate publishing of this type of research. On the other hand, thus taking a more categorical viewpoint, it would be a step forward if we could start a twin register with psychiatric patients in the Netherlands. At the moment, I don't know of any psychiatrist who asks his patient if he or she has a twin brother or sister. A clinical database of "psychiatric" twin pairs could provide us with an overwhelming source of information. We would be able to have a closer look at environmental factors and to estimate heritabilities of diagnoses. A twin register like this can only be started with cooperation of all researchers in this field and with enough funds, but it is an idea well worth trying. If we don't ask patients if they are twins, the remark of Lewis (1935) in the introduction of this thesis will remain true: it is a pity that twins are so rare.

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Samenvatting

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Samenvatting

In dit proefschrift, getiteld, 'Obsessie. De genetische en omgevingsarchitectuur van obsessieve-compulsieve - symptomen', is met behulp van tweelingonderzoek onderzocht in hoeverre obsessieve-compulsieve (OC) symptomen beïnvloed worden door genetische factoren en/of omgevingsinvloeden.

Obsessieve-compulsieve stoornis

Een obsessieve-compulsieve stoornis (OCS) is een complexe psychiatrische stoornis, gekenmerkt door obsessies ofwel dwanggedachten en compulsies ofwel dwanghandelingen. Obsessies zijn steeds terugkerende en hardnekkige gedachten, beelden of impulsen die als opdringend en niet-eigen beleefd worden. Obsessies veroorzaken angst of spanning, die weer geneutraliseerd moeten worden door het uitvoeren van compulsies. Compulsies zijn herhaalde gedragingen of mentale activiteiten, zoals het opzeggen van goede gedachten of het dwangmatig bidden. Deze kennen vaak een ritueel karakter of moeten uitgevoerd worden volgens strikte regels. Veel voorkomende dwanghandelingen zijn wassen, controleren, tellen en verzamelen. De diagnose OCS wordt gesteld als obsessies en compulsies meer dan één uur per dag in beslag nemen en duidelijk hinder geven in het dagelijkse leven. Als dwanggedachten of -handelingen minder dan een uur per dag innemen, maar wel hinder geven of wanneer ze meer dan een uur optreden maar zonder hinder, dan spreekt men van "subthreshold" OCS. OCS komt bij ongeveer 1% van de Nederlanders voor en is daarmee een relatief frequent voorkomende psychiatrische aandoening. Het beloop van OCS kan sterk variëren, maar kent als regel een chronisch beloop.

Tweelingonderzoek

Tweelingonderzoek is een veelgebruikte benadering in gedragsgenetisch en psychiatrisch onderzoek en maakt gebruikt van het feit dat er twee type tweelingen zijn: eeneiige en twee-eiige tweelingen. Eeneiige of monozygote (MZ) tweelingen zijn genetisch identiek, terwijl twee-eiige of dizygote (DZ) tweelingen gemiddeld de helft van hun genen delen. Dit laatste geldt ook voor niet-tweeling broertjes of zusjes. De mate waarin een bepaalde eigenschap erfelijk is, wordt onderzocht door de gelijkenis tussen eeneiige tweelingen te vergelijken met de gelijkenis tussen twee-eiige tweelingen. Deze mate van samenhang wordt statistisch uitgedrukt in een *correlatie*. Een correlatie kan variëren van 0 (geen enkele samenhang) tot en met 1 (volledige samenhang). Als de correlatie in eeneiige tweelingen hoger is dan de correlatie in twee-eiige tweelingen duidt dit erop dat de betreffende eigenschap tenminste voor een deel erfelijk is. Als de correlatie in eeneiige tweelingen gelijk is aan de correlatie in twee-eiige tweelingen, is dat een aanwijzing dat de omgeving die gedeeld wordt door leden uit hetzelfde gezin van belang is, de zogenaamde gedeelde omgevingsinvloeden. Verschillen tussen eeneiige tweelingen worden verklaard door omgevingsfactoren waaraan het ene lid van de tweeling wel is blootgesteld en de ander niet, de zogenaamde unieke omgevingsfactoren.

Het proefschrift bestaat uit vier delen. Hieronder volgt per deel een samenvatting van de bijbehorende hoofdstukken.

DEEL I. INTRODUCTIE IN OCS, OC SYMPTOMEN EN TWEELINGSTUDIES

Hoofdstuk 2 geeft in een kort bestek een overzicht van wat OCS is, de epidemiologie, de stand van zaken op neurobiologisch en genetisch gebied en de behandelingsmogelijkheden.

Hoofdstuk 3 geeft een literatuuroverzicht van meer dan 70 jaar gepubliceerde tweelingstudies die tot nu toe gedaan zijn met OCS of OC symptomen. Vier verschillende fases van tweelingonderzoek van OCS worden beschreven. De *eerste en oudste benadering* zijn casestudies van tweelingen met OCS zonder gebruik te maken van duidelijk omschreven criteria voor OCS. Deze benadering vinden we vooral terug in literatuur uit de jaren 30, 40, 50 en 60 van de twintigste eeuw.
De *tweede fase* behelst studies die gebruik maken van DSM-IV criteria voor OCS. De DSM is het meest gebruikte classificatie systeem voor psychiatrische aandoeningen. De *derde fase* binnen tweelingstudies binnen OCD is de dimensionele benadering, waarbij niet zo zeer naar DSM-IV criteria wordt gekeken, en dus naar patiënten, maar naar het bestaan van OC symptomen binnen de algemene bevolking. Hierbij wordt gebruik gemaakt van vragenlijsten met OC symptomen, die een kwantitatieve score geven. Het voordeel van het werken met kwantitatieve vragenlijsten is dat iedereen (bijvoorbeeld niet aangedane familieleden van OCD patiënten) een score ontvangt. De onderliggende hypothese is dat OC symptomen "normaal verdeeld" onder de bevolking voorkomen en dat OCS voorkomt op het extreme einde van deze normaalverdeling. Redenerend vanuit die veronderstelling, zijn genen die gevonden worden in de algehele populatie tevens verantwoordelijk voor het ontstaan van OCS. Wordt in de derde fase alleen naar correlaties gekeken bij vaak kleine groepen tweelingen, de *vierde fase* kenmerkt zich door gebruik van een dimensionele benadering en moderne analyse methoden bij grote groepen tweelingen met daadwerkelijke schattingen van de erfelijkheidspercentages. Geconcludeerd wordt dat deze laatste methode overtuigend laat zien dat genetische factoren van groot belang zijn bij OCS bij kinderen, met erfelijkheidsschattingen variërend van 45% tot 65%. Bij volwassenen worden erfelijkheidsschattingen gevonden van 27% tot 47%, maar een grootschalige tweelingstudie naar OCS ontbreekt nog.

DEEL II. ERFELIJKHEID, SELECTIEVE PARTNERKEUZE EN CULTURELE TRANSMISSIE

In **hoofdstuk 4** worden de erfelijkheidsschattingen van OC symptomen onderzocht in een groot familie onderzoek bij tweelingen. De Young Adult Self Report (YASR-OCS), een vragenlijst met 8 OC vragen, werd gebruikt om de OC symptomen te meten. De schaal werd eerst gevalideerd en liet bevredigende eigenschappen zien met een sensitiviteit en specificiteit van respectievelijk 82.4 en 69.7%. Van 5893 eeneiige en twee-eiige tweelingen waren ingevulde OC vragenlijsten beschikbaar. Aan deze tweelinggroep werd ook de data van 1304 broers en zussen van tweelingen toegevoegd. Het toevoegen van gegevens van broers en zussen heeft het voordeel dat het beter mogelijk is om statistisch vast te stellen of er effecten zijn van de gedeelde familieomgeving. In deze studie werd geconcludeerd dat de correlaties bij twee-eiige tweelingen en bij broers/zussen overeenkomen. Dit betekent dat twee-eiige tweelingen net zo op elkaar lijken als hun broers of zussen. De resultaten laten zien dat er, afhankelijk van de gekozen statistische index, weinig (39% voor mannen en 50% voor vrouwen) of geen sekse verschillen (47%) in erfelijkheidsschattingen voor OC symptomen zitten. De overige variantie wordt verklaard door unieke omgevingsfactoren. De genetische factoren die OC symptomen veroorzaken lijken hetzelfde te zijn voor mannen en vrouwen.

In **hoofdstuk 5** wordt er gekeken of er een associatie is tussen OCS scores van echtgenoten. Deze resultaten werden vergeleken met die voor angst en depressieve symptomen. Als partners op elkaar lijken op het gebied van OC symptomen kan dit belangrijk zijn omdat één van de veronderstellingen binnen tweelingstudies is dat partners keuze random is met betrekking tot de eigenschap die wordt bestudeerd. Zo niet, dan kan die eigenschap tot verhoogde genetische overeenkomst tussen bijvoorbeeld (tweeling)broers en zussen leiden, terwijl we uitgaan van een gemiddelde van 50% overeenkomst in genetisch materiaal. Er werden 1400 tweelingen en hun partners onderzocht en 850 ouders (ouderparen) van tweelingen. Er werd een significante correlatie gevonden van .15 tussen partners voor OC symptomen bij zowel de ouders van tweelingen, als bij tweelingen en hun partners. Dit wijst er in elk geval op dat lengte van huwelijk of samenzijn, ouders zijn immers al langer bij elkaar dan hun kinderen, zijn geen invloed heeft op de hoogte correlatie van de partners voor OC symptomen. Door correlaties tussen partners, correlaties tussen tweeling en partner van tweelingbroer of zus, en correlaties tussen beide partners van tweelingen (dus partner tweeling één met partner tweeling twee) met elkaar te vergelijken, kun je iets zeggen over de mogelijke oorzaken van de gevonden partner correlaties. Kiezen partners elkaar bewust uit op een eigenschap (*phenotypic assortment*)? Gaan partners meer op elkaar lijken tijdens het huwelijk (*marital interaction*)? Of kiezen partners elkaar uit omdat ze binnen bepaalde sociale kringen verkeren waarin een bepaalde eigenschap verhoogd voorkomt (*social homogamy*)? Zoals gezegd vonden we voor "marital interaction" weinig aanwijzingen. Het bleek dat we voor de andere verklaringen de correlaties te laag waren om goed onderscheid te maken tussen de verklaringsmechanismen. Wel is de totale correlatie voor OC symptomen tussen partners zodanig laag, dat dit nauwelijks invloed heeft op erfelijkheidsschattingen. Deze conclusie geldt ook voor angst en depressieve symptomen.

Hoofdstuk 6 geeft een studie weer met de erfelijkheidsschattingen van OC symptomen, dit keer met 12 vragen van de OC schaal PI-R ABBR. Bijzonder aan deze studie is dat naast gegevens van tweelingen (4408 in aantal) en de broers en zussen van de tweelingen (in totaal 1309) ook de gegevens van ouders van tweelingen (2305 in aantal), gebruikt werden in de analyses. Daardoor kon ook worden gekeken naar het bestaan van culturele transmissie. Culture transmissie is het fenomeen dat ouders zorgen voor een gezinsomgeving die, los van de erfelijke beïnvloeding, OC symptomen versterken bij hun kinderen. Bij vrouwen werd een erfelijkheidsschatting gevonden van 37%, was er geen invloed van culturele transmissie en de overige variantie werd verklaard door unieke omgevingsfactoren. Bij de mannen vonden we verrassende, in het licht van het gehele proefschrift ook onverwachte, resultaten met een minieme maar significante invloed van culturele transmissie naast het bestaan van genetische factoren. Er werd daarnaast een grote invloed (27%) gevonden van de gedeelde omgeving. De overige variantie werd verklaard door unieke omgevingsinvloeden (71%). De gevonden gedeelde omgeving voor OC symptomen is niet eerder gevonden bij volwassenen tweelingstudies en wordt veroorzaakt door

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relatief hoge correlatie bij mannelijk twee-eiige tweelingen. Gezien het feit dat de groep mannelijke twee-eiige tweelingen relatief klein was, kan de vraag gesteld worden of deze bevinding niet op toeval berust. Toekomstig onderzoek zal dit moeten uitwijzen.

DEEL III. INVLOED VAN GENEN EN OMGEVING OP OC SYMPTOMEN OVER DE TIJD

Doel van de studie in **hoofdstuk 7** was om de stabiliteit, ofwel persistentie, van OC symptomen te bekijken bij kinderen en nader te onderzoeken in hoeverre deze stabiliteit beïnvloed werd door genen of omgeving. Er werd gebruik gemaakt van zowel vader- als moederbeoordelingen van hun kinderen op het gebied van OC symptomen. Hiervoor werd de OC schaal uit de Child Behavior Checklist (CBCL-OCS) gebruikt, bestaande uit 8 vragen. Door zowel naar vader- als moederbeoordelingen te kijken kon gebruik worden gemaakt van overeenkomst tussen deze beoordelingen waarmee een hoge mate van betrouwbaarheid werd verkregen. In totaal werden data op drie verschillende leeftijden (tweelingen op de leeftijd van 7, 10 en 12 jaar) van in totaal 8083 families geanalyseerd. Er werd een onderlinge correlatie over de tijd gevonden tussen OC symptomen van .50. Dit duidt op een redelijke stabiliteit van OC symptomen. Deze stabiliteit werd veroorzaakt door invloeden van zowel genen (ruwweg 35%) als omgeving (65%), waarbij binnen de omgeving zowel gedeelde als unieke omgevingsfactoren een even grote rol speelde.

Hoofdstuk 8 onderzocht de invloeden van genen en omgeving op OC symptomen tijdens de puberteit op de leeftijd van 12, 14 en 16 jaar. Er werd gebruik gemaakt van de OC schaal uit het Youth Self Report (YSR-OCS). Deze lijst komt overeen met de CBCL-OCS, met dit verschil dat de YSR-OCS door de tweelingen zelf werd ingevuld en niet door de ouders. Op leeftijd van 12 jaar werd er geen verschil gevonden tussen de hoeveelheid OC symptomen voor meisjes en jongens, maar op leeftijd van 14 en 16 jaar lieten meisjes meer symptomen zien dan jongens. Genetische invloeden werden op alle leeftijden gevonden met schattingen respectievelijk 27%, 57%, en 54% op 12, 14 en 16 jaar. De invloed van een gedeelde omgeving (16%) werd alleen gevonden op 12-jarige leeftijd. De overige variantie werd verklaard door unieke omgevingsfactoren.

In **hoofdstuk 9** onderzochten we de stabiliteit van OC symptomen en de genetische en omgevingsbijdragen aan deze stabiliteit in volwassenen. YASR-OCS data van eeneiige en twee-eiige tweelingen uit het vragenlijstonderzoek van 1991, 1995 en 1997 werden gebruikt voor deze longitudinale analyses plus PI-R ABBR data uit 2002. De correlaties tussen de tijdstippen varieerden tussen .39 en .61. Deze stabiliteit werd door 70% veroorzaakt door genetische factoren. Daarnaast werden er hoge genetische correlaties tussen de tijdstippen gevonden. Dit duidt erop dat dezelfde genen verantwoordelijk zijn voor OC symptomen over de tijd. Deze bevindingen zijn belangrijk voor verder onderzoek, want dit betekent dat volwassenen van verschillende leeftijden tegelijkertijd onderzocht kunnen worden in studies waarin daadwerkelijk naar genen wordt gezocht voor OC symptomen.

DEEL IV. OMGEVINGSFACTOREN EN SYMPTOOMDIMENSIES VAN OC SYMPTOMEN

In **hoofdstuk 10** is onderzocht welke omgevingsfactoren beschermen tegen OC symptomen of juist OC symptomen veroorzaken. Hiervoor werd een bijzondere onderzoeksmethode gebruikt: het discordante monozygote tweelingdesign. Discordant betekent dat het ene lid van een eeneiige tweeling wel OC symptomen heeft en de andere niet of weinig. Deze discordantie kan worden verklaard vanuit unieke omgevingsfactoren die de ene tweeling wel heeft beleefd en de andere niet. Op basis van de PI-R ABBR werden 25 discordante eeneiige tweelingparen geselecteerd. Tevens werd een groep eeneiige tweelingen geselecteerd, waarvan beide hoog scoorden (concordant hoog, 17 paren) en een groep waarvan beide eeneiige tweelingen laag scoorden (concordant laag, 34 paren). Door de concordant hoge groep te vergelijken met de concordant lage groep is het ook mogelijk om omgevingsfactoren die OC symptomen beïnvloeden te onderzoeken. Deze omgevingsfactoren worden in tegenstelling tot de discordante tweelingmethode gedeeld door beide tweelingen. Binnen de discordante groep was het opvallend dat seksueel misbruik veel voorkwam bij de hoog scorende tweelingen. Verder was het geboortegewicht van de discordante groep lager dan dat van de concordant hoog scorende tweelingen. Ook vonden we dat concordant hoog scorende tweelingen relatief lager opgeleid waren en minder vaak een religieuze achtergrond hadden of naar de kerk gingen dan de laag scorende concordante tweelingen. Kijken we naar eerdere metingen binnen het tweelingregister dan valt op dat de concordant hoge groep al vroeg OC symptomen vertoont en de discordante groep relatief laat discordant geworden zijn. Dit bevestigt de genetische invloed van bij het vroeg ontstaan van OC symptomen.

In **hoofdstuk 11** is de erfelijkheidsschatting onderzocht van OC dimensies. Eerder onderzoek geeft aanwijzingen dat OC symptomen te verdelen zijn in verschillende clusters of factoren van symptomen, zoals symptomen rondom het cluster controleren of cluster wassen. In deze studie werden 1383 vrouwelijke tweelingen van het Virginia Twin Registry onderzocht. OC symptomen waren gemeten met behulp van 20 vragen van de Padua Inventory. Na factor analyse werden drie factoren gevonden: ruminatie (herhalen van gedachten), smetvrees/wassen en controleren. In een “multivariate” (alle factoren werden tegelijkertijd meegenomen) analyse werden verschillende modellen onderzocht om te zien welk model het beste bij de data paste. Uit deze analyses kwam een universele OC symptomen factor naar voren die op zijn beurt de diverse specifieke OC clusters of factoren beïnvloedt. Deze universele OC symptomen factor wordt door zowel genen (36%) als unieke omgevingsfactoren (74%) beïnvloed. In tegenstelling tot de factoren ruminatie en controleren, wordt smetvrees ook nog beïnvloed door specifieke (onafhankelijk van de universele factor) genetische en omgevingsfactoren.

Het is nog maar relatief kort geleden dat genetische oorzaken voor OCS niet ter sprake kwamen in de spreekkamer van de psychiater. Sterker nog, oorzaken werden vooral in omgevingsfactoren gezocht, bijvoorbeeld in de opvoedingstijlen van ouders. Dit proefschrift laat zien dat, zowel tijdens de kindertijd als volwassenentijd, genetische als wel omgevingsfactoren van cruciaal belang zijn voor het ontstaan van OCS.

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van Grootheest, D. S., van den Heuvel, O. A., Cath, D. C., van Oppen, P. & van Balkom A. J.: Obsessieve-Compulsieve Stoornis. *Ned Tijdschr Geneeskd,* (accepted).

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Als laatste mijn kamergenoten waarmee het altijd goed en gezellig toeven was. Eske, voor wie statistiek geen geheimen kent. Tinca, altijd vrolijk en energiek en nu zelfs paranimf!

Curriculum Vitae

Daniël Sebastiaan van Grootheest werd op 29 mei 1973 in Amsterdam geboren. Na een jaar vertrok hij met zijn ouders naar Zaïre, de huidige Democratische Republiek Congo, waar hij drie jaar woonde. Zijn verdere jeugd bracht hij, inmiddels met 2 jongere zussen (geen tweeling!), door in Veenendaal, waar hij in 1991 zijn VWO afrondde. Vervolgens studeerde hij geneeskunde aan de Vrije Universiteit te Amsterdam. Tijdens zijn studie volgde hij een wetenschappelijke stage onder supervisie van psychiater Aartjan Beekman bij de Longitudinal Aging Study Amsterdam. Hij bestudeerde daar de effecten van 'verweduwing' bij mannen op depressie, hetgeen leidde tot zijn eerste wetenschappelijke publicatie. In 1999 haalde hij zijn artsenbul en werkte daarna een jaar als arts-assistent psychiatrie in het psychiatrische ziekenhuis Duin & Bosch te Castricum. Hierna werkte hij als onderwijscoördinator voor de vakgroep psychiatrie van de VU. Hij startte vervolgens in 2001 met de opleiding tot psychiater bij GGZ Buitenamstel in Amsterdam. In 2004 startte hij zijn promotieonderzoek naar obsessieve-compulsieve symptomen bij de afdeling Biologische Psychologie (VU). Dit onderzoek vond plaats in samenwerking met de afdeling Psychiatrie (VU). In 2008 hoopt hij zijn opleiding tot psychiater af te ronden. Naast zijn opleiding en onderzoek, is hij sinds 2007 betrokken bij Anno73, een bedrijf dat medische websites verzorgt. Hij is de partner van Liesje van Leeuwen en samen hebben ze twee kinderen: Crispijn (2005) en Jonathan (2007).

Daniël Sebastiaan van Grootheest was born on May 29th, 1973 in Amsterdam. After living in Amsterdam for a year he moved with his parents to Zaire, nowadays called Democratic Republic Congo, where they stayed for three years. He grew up with two younger sisters (no twins!) in Veenendaal for the remaining part of his childhood. He graduated from high school in 1991, and subsequently started his study at the Medical school at the VU University in Amsterdam. In 1997 he attended a scientific internship with psychiatrist Aartjan Beekman at the Longitudinal Aging Study Amsterdam examining the effects of bereavement in men, which resulted in his first scientific publication. In 1999, he graduated as MD and worked one year as a resident of psychiatry in the former psychiatric hospital Duin & Bosch in Castricum. This was followed by a job as coordinator of education at the Department of Psychiatry of the VU University Amsterdam. In October 2001 he started his training as a psychiatrist at GGZ Buitenamstel in Amsterdam. His twin research on obsessive-compulsive symptoms started three years later (2004) at the Department of Biological Psychology in collaboration with the Department of Psychiatry. This year he hopes to finish his training as a psychiatrist. In addition to his training and research, he is since 2007 partner of Anno73, a company that publishes medical websites. He lives with Liesje van Leeuwen, and has 2 children, Crispijn (2005), and Jonathan (2007).